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INFANTILE CORTICAL HYPEROSTOSIS*

AN INQUIRY INTO ITS FAMILIAL ASPECTS

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INFANTILE cortical hyperostosis is a disease of infants which is characterized by the formation of cortical subperiosteal new bone in one or more bones of the body. Pain and soft tissue swelling over the affected parts, associated with fever and irritability, are found frequently with the disease. Usually self-limiting, it is not as a rule followed by any residual skeletal deformity.

HISTORICAL REVIEW

In 1945 Caffey and Silverman[5] described and named this condition. This was followed in 1946 by a report by Smyth, Potter and Silverman[17] of a series of similar cases which had been collected independently. Current interest in this condition stems from these reports.

Prior to 1945 there were descriptions of certain infantile bone lesions which in all probability would now be classified as infantile cortical hyperostosis. West[19] in 1888 reported cases in siblings which might be explained by the syndrome of infantile cortical hyperostosis but, since this was seven years before Röntgen's epoch-making discovery, roentgenographic evidence was not available. Roske[13] in 1930 and Ellis[11] in 1939 also reported cases that probably now would be classified as infantile cortical hyperostosis. In 1939 Caffey[4] described an undiagnosed bone lesion which, with Silverman, he later reported, together with 3 additional cases, as the basis of the classic description referred to above.

Although prior to 1946 there are only a few case reports that can be placed in this category, since that time cases have been reported with increasing frequency. In 1950 Sherman and Hellyer[14] reviewed all of the roentgenograms in their files for the previous twenty years and failed to locate a single case that could be classified as infantile cortical hyperostosis. It may be inferred from this study that the paucity in the number of case reports prior to 1946 was not due entirely to mistaken diagnoses, but

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that either the disease is an old disease, the frequency of which is increasing, or it is a new entity.

Cayler and Peterson[10] found 17 cases in the six and one half years preceding their report of 1956; their experience suggests an incidence in practice of 3 cases per 1,000 patients under six months of age registered in hospitals and clinics. They also suggest that many cases are overlooked because they may be asymptomatic.

In the reported cases the disease has been found to affect equally rich and poor, male and female, and it has been seen in practically every nationality and in every race.

CLINICAL COURSE

While different cases vary in minor details, there are certain more or less characteristic features that are present in a large proportion of those reported. The disease usually appears in early infancy, the average age of onset being about ten weeks. It is occasionally manifest at birth[12] and has been seen in the unborn fetus.[1,2] Onset after the age of five months is so rare that, according to Caffey,[7] initial manifestations after this age should raise a question as to the diagnosis.

Initial symptoms and signs are usually abrupt. A child who previously has been well develops fever, irritability and one or more painfully swollen areas. Swelling occurs over the mandible in about 75 per cent of the reported cases; swellings may occur over the long bones either with or without associated mandibular involvement. Next to the mandible in frequency are the ulnae, clavicles, ribs, radii, tibiae, femora, scapulae and fibulae in about that order.

It is the experience of the present authors and of others that there are many cases in which the clinical symptoms are so mild or atypical that they easily may be overlooked by both the parents and the physicians.

ROENTGEN FINDINGS

If a patient suspected of having the disease is studied roentgengraphically, subperiosteal cortical thickening of the bones will be found beneath areas of soft tissue swelling and often elsewhere. This is usually present at the time of the initial examination but, if not, it may appear within about two weeks. Raised periosteum may extend along the entire shaft but rarely, if ever, does it extend beyond the metaphysis. In the early stages the marrow cavity appears to be somewhat encroached upon by dense cortical bone. The return to normal seems to vary in different cases. In some cases the subperiosteal new bone appears to decrease progressively over the months by an absorptive process until the normal contour of the bone remains. In other cases marrow tissue appears to extend beyond the old cortex into the new bone, so that the marrow cavity extends as far as the edge of the new bone. The old cortex is replaced by marrow tissue and the edge of the new bone forms a new cortex with compact bone. This results in an apparent expansion of the marrow cavity for a period of time.

Quite often there is an unequal deposition of new bone on the shafts of involved long bones. In the tibia there is usually greater deposition of new bone on the anterior surface than on the posterior, lateral or medial surfaces and, consequently, when retubulation has been completed, marked anterior bowing results. This may remain for several months after the subperiosteal cortical bone has been completely replaced by marrow tissue. This bowing deformity exists between the ages of seven months and one year.

Between the ages of one and three years, straightening of the bowing deformities usually takes place so that by the age of three years there is usually little or no trace of the disease.

Caffey[6,9] has described several cases with late skeletal manifestations.

THERAPY

The disease does not appear to be influenced to any appreciable extent by any known therapy.

Treatment is primarily symptomatic.

Analgesics such as aspirin and sedatives as, for instance, phenobarbital are usually adequate for controlling pain and discomfort. Caffey[7] has suggested the use of steroids, feeling that the likelihood of bowing and other late deformities might be lessened. Sidbury and Sidbury[15] believe that such therapy carries with it a certain risk and should be reserved for only the very seriously ill patients.

ETIOLOGY AND FAMILIAL INCIDENCE

Although the number of case reports of infantile cortical hyperostosis is rapidly increasing, and in spite of the fact that the disease is being recognized in pediatric practice so frequently that only cases of unusual interest are now being published, the etiology and pathogenesis are still poorly understood. Thought at first to be probably of infectious origin, to date no bacterial or viral agents have been isolated as causative factors. Trauma, allergies and endocrinopathy have never been proved as being related to the disease.

Recently there has been interest in the familial aspects of infantile cortical hyperostosis. In 1948 Van Zeben[18] reported 3 cases occurring in two siblings and a cousin. In 1951 Boyes and Demy[3] reported the disease in a brother and sister; from the history elicited, the condition may have occurred also in the maternal grandfather for it was said that he was "very bowlegged." In 1953 Barba and Freriks[1] and in 1954 Sidbury and Sidbury[15] described the disease in siblings.

Since infantile cortical hyperostosis has been demonstrated in the fetus *in utero*[1,2] and also in a child within hours after birth,[12] and since this is a disease of early infancy, the supposition that this may represent a trait carried by the genes is all the more plausible.

The present authors believe that evidence derived from their observations of a family showing the manifestations of this disease in 11 members over a period of fourteen years lends support to an hereditary factor in the etiology of the condition (Fig. 1).

REPORT OF CASES

Case 1. E.L. On July 25, 1945 a three week old female child was admitted to the deGoesbriand Memorial Hospital with the chief complaint of "crying when the legs were extended." The child was in so much pain that the mother had to lift her by the buttocks. The pregnancy had been uneventful and there was no feeding problem. There were 5 older children, the oldest nine and the youngest three years of age. These

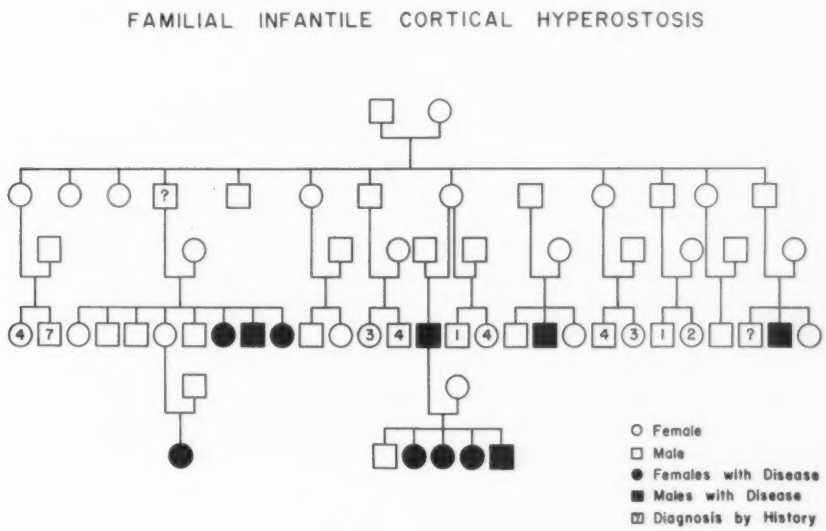

Fig. 1. Incidence of infantile cortical hyperostosis occurring in one family in a fourteen year period.

Fig. 2. Case 1. E.L. Age, three weeks. There is subperiosteal cortical thickening of both tibiae and both femora.

were all living and well and no history could be elicited of abnormalities at birth or in early infancy.

The physical examination revealed a well-nourished infant who was irritable and fretful and cried when any attempt was made to move her. Both legs were swollen and warm to the touch. The soft tissues over the femora were painfully swollen but not to the same degree. The blood count showed white blood cells 22, 100, 42 per cent neutrophils, 47 per cent lymphocytes, 10 per cent monocytes, 1 per cent cosinophils. The rectal temperature was 99.4°F.

Roentgenograms of the lower extremities (Fig. 2) showed that there was marked subperiosteal cortical thickening of both tibiae and associated anterior bowing. On the lateral aspects of both femora in the proximal portions there was subperiosteal cortical thickening. Only slight anterior bowing of the legs was evident.

Repeat examination at four months of age (Fig. 3) showed that, since the previous examination, there had been an apparent decrease in subperiosteal cortical thickening of the tibiae, whereas the thickening of the femora had increased. The femoral cortical elevations at this time extended almost the entire length of the diaphysis on the lateral aspects but did not cross the epiphyseal plates either proximally or distally. The anterior bowing of the femora had increased somewhat.

Roentgenographic examination at the age of seven months (Fig. 4) showed that there had been moderate improvement in the amount of subperiosteal elevation, especially in both tibiae. Regression was also noted in the femora where subperiosteal cortical elevation was seen only in the middle thirds of the bones. Anterior bowing was still present.

Roentgenograms at the time of discharge at ten months of age (Fig. 5) showed marked improvement. Only a trace of cortical thickening was noted in each tibia and there was only a slight degree of anterior bowing remaining, more marked on the left than on the right. There was also improvement in the cortical thickening of the femora, only a small amount remaining on the convex surfaces. Moderate bowing still remained in these bones.

At the end of three years a roentgenographic examination showed that all of the cortical thickening had disappeared (Fig. 6). No definite residual deformity could be seen.

Roentgenographic examination at the age of fourteen years (Fig. 7) revealed the tibiae and the femora to be within normal limits.

Fig. 3. Case 1. E.L. Age, four months. The subcortical periosteal thickening of the tibiae has apparently decreased while that of the femora has increased. Tibial bowing is present.

Fig. 4. Case 1. E.L. Age, seven months. Regression of the subperiosteal cortical thickening of both the tibiae and the femora. Anterior bowing involves both the tibiae and the femora.

Fig. 5. Case 1. E.L. Age, ten months. Only a trace of subperiosteal thickening remains in both tibiae and femora. There is slight bowing of both femora and tibiae.

Case II. G.L. On March 15, 1947 a six month old child, a brother of Case 1, was brought as an outpatient to the radiology department of the deGoesbriand Memorial Hospital because of painful swellings of the arms and legs.

Roentgenographic examination at that time showed subperiosteal cortical thickening of both radii, both femora and both tibiae (Fig. 8, *A* and *B*).

Roentgenographic examination at the age of one year (Fig. 9) revealed that the right femur was normal but that the left exhibited a moderate degree of bowing. The examination of both tibiae showed that there was still slight cortical thickening and bowing.

An examination performed in 1959 when the patient was twelve years of age (Fig. 10 and 11) revealed no residual deformity in either femur or in the bones of the legs.

Case III. Mary L. On May 25, 1948 a four and one half month old female, a sister of Cases 1 and II, was brought as an outpatient to the radiology department of the deGoesbriand Memorial Hospital with the chief complaint of painful swelling of both legs and thighs.

Roentgenograms were taken of both lower extremities and of both forearms (Fig. 12, *A* and *B;* 13, *A* and *B*). There was a marked increase in the transverse diameters of the tibiae, involvement being about equal on each side. The increase in the transverse diameter of the bones was obviously due to subperiosteal cortical thickening which did not extend beyond the epiphyseal plates. In addition, there was a rather marked degree of anterior bowing and some soft tissue swelling. The femora had a somewhat similar appearance but the subperiosteal thickening did not involve the bones as uniformly as in the tibiae. The involvement was less symmetric, being greater on the convex than on the concave surfaces. Anterior bowing was also present. Examination of the forearms showed moderate subperiosteal cortical thicken-

Fig. 6. Case I. E.L. Age, three years. Roentgenographic appearance of both femora and both tibiae is within normal limits.

ing of the distal thirds of both radii.

No other parts of the body were examined roentgenographically but there were no symptoms to suggest involvement of other bones. There was no mandibular swelling.

A roentgenogram of both legs in 1959 (Fig. 14, *A* and *B*) when the child was eleven years of age, revealed no residual deformity of either tibia.

Case IV. Michael L. On May 14, 1952 a three month old male infant was sent to the radiology department of the deGoesbriand Memorial Hospital. Three weeks previously the child had fallen from his crib and since that time he had been "fussy and cranky." Swelling had appeared over his left leg and had become progressively worse.

Anteroposterior (Fig. 15) and lateral roentgenograms of the left lower extremity revealed subperiosteal new bone formation of a considerable degree involving the middle portion of

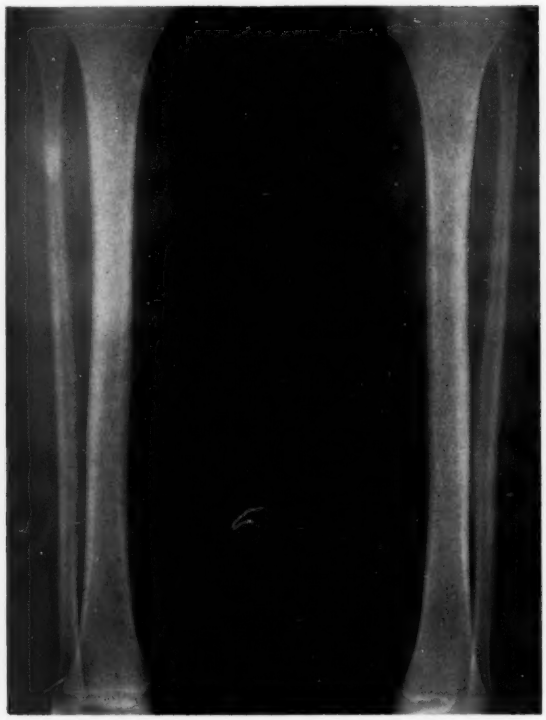

Fig. 7. Case I. E.L. Age, fourteen years. Roentgenographic appearance of both tibiae is within normal limits.

the left tibia with anterior bowing of the shaft. No evidence of fracture could be seen.

Examination of other bones disclosed subperiosteal cortical thickening of the medial ends

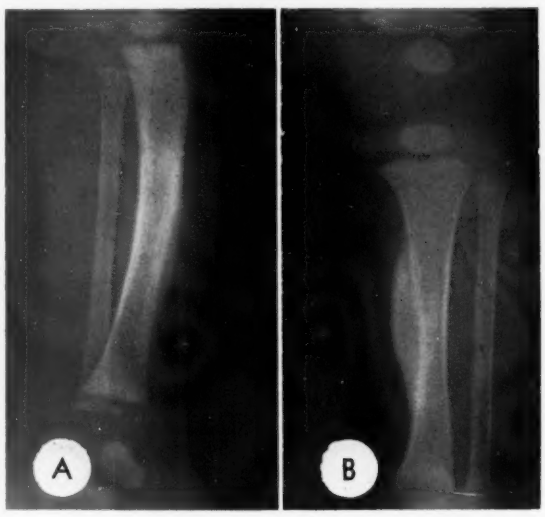

Fig. 8. Case II. G.L. Age, six months. (*A* and *B*) Subcortical periosteal cortical thickening on the medial side of the midshaft of the left tibia.

Fig. 10. Case II. G.L. Age, twelve years. Both tibiae are within normal limits.

Fig. 9. Case II. G.L. Age, one year. Slight subperiosteal cortical thickening of both tibiae; lateral bowing of the left femur.

Fig. 11. Case II. G.L. Age, twelve years. Both femora are within normal limits.

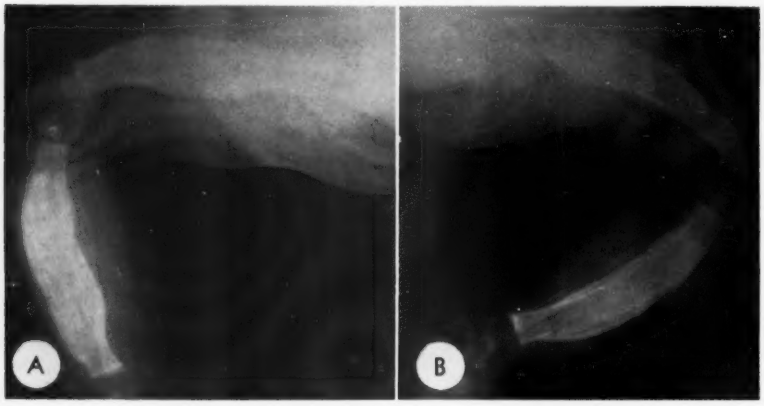

Fig. 12. Case III. Mary L. Age, four and one half months. (*A* and *B*) Marked subperiosteal cortical thickening of both femora and tibiae, with anterior bowing of both tibiae.

of both clavicles, more prominent on the left than on the right side. There was very slight involvement of the right humerus but none of the left. There was also slight involvement of both radii and of the mandible.

Re-examination at the age of six years showed no residual abnormalities (Fig. 16).

Inquiry into the family history disclosed that this child was a first cousin of Cases I, II and III (Fig. 1).

Case V. N.L. On May 24, 1952 a five month old infant was admitted to the pediatric service of the deGoesbriand Memorial Hospital. One day prior to admission, the mother noticed that the child was very irritable and seemed feverish. However, the axillary temperature taken at home was only 98°F. A cough developed simultaneously with the other symptoms.

Fig. 13. Case III. Mary L. Age, four and one half months. (*A* and *B*) Subperiosteal cortical thickening of both radii.

On admission, rectal temperature was 102°F., pulse 145 and respiration 40. Physical examination revealed slight asymmetry of the head and a swelling of the mandible on the right. On palpation a firm area of induration was felt at the angle of the mandible. Pressure over this

Fig. 14. Case III. Mary L. Age, eleven years. (*A* and *B*) Both tibiae are within normal limits.

Fig. 15. Case iv. Michael L. Age, three months. Subperiosteal cortical thickening of the left tibia. (Right tibia was normal.)

Fig. 16. Case iv. Michael L. Age, six years. Both lower extremities are within normal limits.

area caused the infant to cry. There was slight pharyngeal injection, and dullness to percussion was noted over the right upper lung field. The tentative admission diagnosis was acute bronchitis or atypical pneumonia.

Roentgen examination of the chest revealed enlargement of the middle third of the left clavicle (Fig. 17) and involvement of the mandible; a portion of the left humerus that was included on the roentgenogram also showed some cortical thickening. The lung fields were clear and the cardiac silhouette was believed to be within normal limits. On the basis of this chest roentgenogram, the possibility of infantile cortical hyperostosis was suggested and roentgenographic examinations were made of other bones. They revealed that there was characteristic involvement of the left humerus and the radii (Fig. 18, *A* and *B*).

The laboratory findings included a normal urinalysis, hemoglobin of 12 gm. per cent, an erythrocyte count of 4.6 million, leukocytes 8,700, 32 per cent neutrophils, 62 per cent lymphocytes and 6 per cent monocytes. The temperature returned to normal on the second hospital day and the child was taken home on the third hospital day against advice.

Upon further investigation it was discovered that this patient was a first cousin to Cases i, ii, iii and iv.

Fig. 17. Case v. N.L. Age, five months. Expansion of the middle third of the left clavicle.

Fig. 18. Case v. N.L. Age, five months. (*A* and *B*) Subperiosteal cortical thickening on the lateral side of the left humerus and on the ulnar side of the left radius. The epiphyseal plate of the left radius is somewhat distorted.

Fig. 19. Case vi. H.P. Age, twenty-five years. The left femur shows a marked degree of lateral bowing.

Fig. 20. Case vi. H.P. (*A* and *B*) There is a double bow involving both tibiae, medially in the proximal thirds and laterally in the middle thirds. Cortical thickening of the lateral surface of the left tibia appears to be of the stress reaction type.

Case vi. H.P. This patient was a nonsymptomatic twenty-five year old male, who was first seen at the deGoesbriand Memorial Hospital on April 19, 1959. He is a first cousin of the preceding 5 cases. His older brother and sisters stated that he had had swollen extremities as a child but the patient had never been examined roentgenographically until this admission. Marked bowing of the extremities, present in infancy and childhood, had persisted into adult life.

Roentgen examination of the lower extremities showed a marked lateral bowing of the left femur (Fig. 19) with thickening of the cortex on its medial side resembling a stress reaction. The lateral cortex was of normal thickness. Similar changes were noted on the right femur. There was a double bow involving both tibiae (Fig. 20, *A* and *B*). In the proximal thirds the bowing was medial and in the middle thirds it was

lateral. The cortical thickening of the lateral surface of the left tibia appeared to be of the stress reaction type. Roentgenogram of the right humerus (Fig. 21), showed localized cortical thickening of the lateral aspect slightly below the insertion of the deltoid tendons, and a similar change was also observed on the right side. Except for the slight convexity, the alignment of the humeri was straight. There was moderate cortical thickening of both radii and ulnae (Fig. 22, *A* and *B*) with ventrolateral bowing of the former and dorsomedial bowing of the latter.

The roentgenographic findings in this case are not pathognomonic of any single condition. However, the history suggests that the patient may have had infantile cortical hyperostosis in early childhood. Inasmuch as he is a first cousin of the previously described cases and the father of 3 children subsequently studied and shown to have characteristic stigmata of infantile cortical hyperostosis, and since Caffey has described bone changes of infantile cortical hyperostosis persisting into later life, it seems reasonable to suggest that this patient did have the disease in childhood, and that his skeletal deformities are the result of the active phase of the disease.

Fig. 21. Case vi. H.P. Localized cortical thickening on the lateral aspect of the middle third of the right humerus.

Fig. 22. Case vi. H.P. (*A* and *B*) Slight cortical thickening of both radii. There is ventrolateral bowing of the radii and dorsomedial bowing of the ulnae. Radial joint surfaces are tilted in a manner similar to that seen in Madelung's deformity.

Case vii. K.P. A three month old daughter of Case vi was seen at the Mary Fletcher Hospital Pediatric Clinic on June 25, 1956 with the chief complaint of painful, tender swelling of the right leg. The child's prenatal and birth history was uneventful. No areas of soft tissue swelling were observed on physical examination other than that noted over the right tibia.

Roentgen examination of the lower extremities (Fig. 23) demonstrated that there was marked subperiosteal cortical thickening on the medial borders of the tibiae. The femora and fibulae were uninvolved. A roentgenogram of the skull (Fig. 24) revealed evidence of sub-

Fig. 23. Case vii. K.P. Age, three months. Marked subperiosteal cortical thickening of the medial borders of both tibiae; the femora and fibulae are uninvolved.

periosteal cortical new bone formation involving both the right and left sides of the body of the mandible. On an anteroposterior chest roentgenogram the middle third of each clavicle showed a localized fusiform zone of subperiosteal cortical thickening more prominent on the superior than on the inferior surface (Fig. 25). This gave the appearance of a superior bow to the upper surface of the clavicle without accompanying bowing of the inferior surface. Examination of each arm and forearm showed cortical thickening of both humeri and ulnae.

Fig. 24. Case vii. K.P. Age, three months. Subperiosteal cortical thickening involving the body of the mandible on both the right and the left sides.

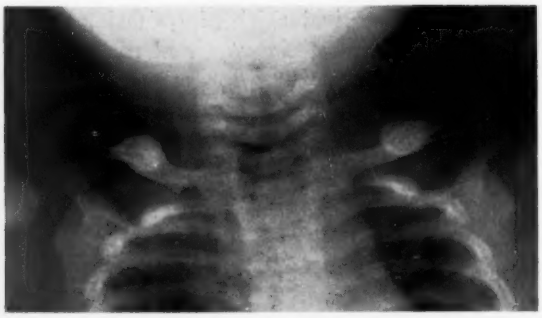

Fig. 25. Case vii. K.P. Age, three months. Fusiform zones of subperiosteal thickening on the superior surfaces of both clavicles.

Repeat roentgenograms one month later (Fig. 26 and 27), when the child was four months of age, showed that the bony abnormalities had partially but not fully regressed. Roentgenographic examination at the age of three years revealed that the mandible and tibiae had been restored to normal anatomic contour (Fig. 28 and 29).

Case viii. J.P. A sister of Case vii and daughter of Case vi and a first cousin once removed of Cases i, ii, iii, iv and v was born at the Porter Hospital, Middlebury, Vermont, in June, 1957 after a normal pregnancy and delivery. In view of the strong family history of infantile cortical hyperostosis, roentgenograms

Fig. 26. Case vii. K.P. Age, four months. Fusiform swellings of both clavicles have partially regressed.

Fig. 27. Case VII. K.P. Age, four months. Subperiosteal cortical thickening of both tibiae has partially regressed.

Fig. 29. Case VII. K.P. Age, three years. Except for slight bowing of the medial cortices of the tibiae, the contour of the bones is within normal limits.

were taken twenty-four hours after delivery.

A roentgenogram of the skull (Fig. 30) showed marked subperiosteal cortical thickening of the entire body of the mandible and of the rami to a lesser degree. The condyloid processes were uninvolved. Both clavicles showed fusiform enlargement. Examination of the forearms demonstrated marked subperiosteal cortical thickening of both radii (Fig. 31, *A–D*). The thickening on the medial sides of the proximal halves of the bones and on the lateral sides of the distal halves of the bones gave a double bow appearance to these structures. This bowing was quite real and not just an illusion produced by the subperiosteal thickening, since the distal radial articulations were angulated medially

Fig. 28. Case VII. K.P. Age, three years. The mandible now is normal in appearance.

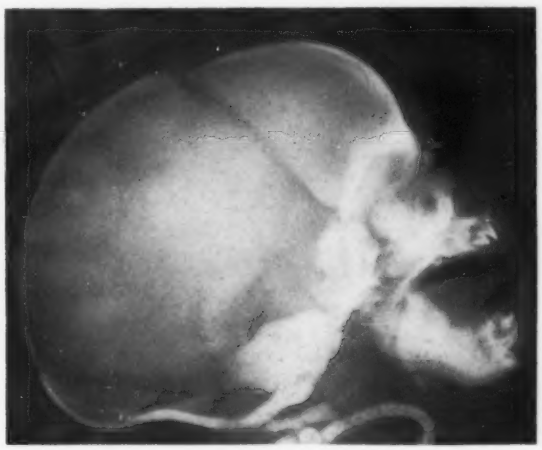

Fig. 30. Case VIII. J.P. Newborn. Subperiosteal cortical thickening of the body and both rami of the mandible.

Fig. 31. Case VIII. J.P. Newborn. (*A* and *B*) Right and (*C* and *D*) left side. Marked subperiosteal cortical thickening of both radii. The distal halves of the bones have a double bowed appearance.

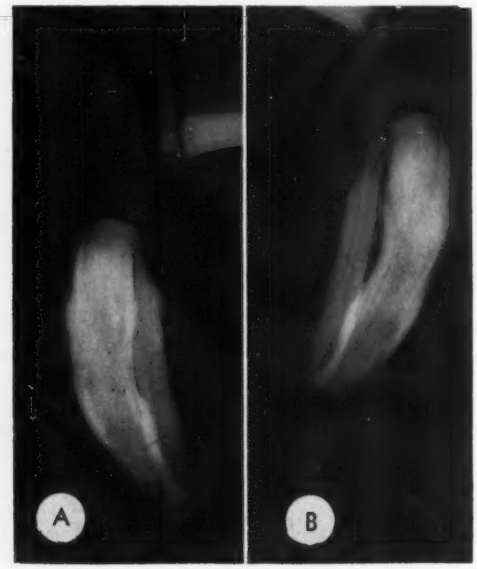

Fig. 32. Case VIII. J.P. Newborn. (*A* and *B*) Marked subperiosteal new bone formation of both tibiae and fibulae.

Fig. 33. Case VIII. J.P. Age, six months. (*A* and *B*) Lateral views. Marked anterior bowing of the tibiae without evidence of subperiosteal cortical thickening at this time. The medullary portions appear to be larger than normal. The fibulae are straight.

about 45 degrees, while the uninvolved ulnae showed no deviation of the distal articulations. Roentgenograms of both legs (Fig. 32, *A* and *B*) showed marked subperiosteal new bone formation of both the tibiae and the fibulae. The thickening of the tibiae was for the most part on the anterior surfaces of the bones with marked anterior bowing; on the other hand, the thickening of the fibulae was on the posterior surfaces, with no associated bowing. The other skeletal structures of the body were not involved to any appreciable extent.

During the ensuing six months the child grew normlly, seemed to have relatively little pain, but had slight soft tissue swelling of both legs. Roentgenography at the age of six months revealed considerable regression of all bony changes. On examination of the legs, practically all of the cortical thickening was seen to have disappeared, but there was still marked anterior bowing of the tibiae (Fig. 33, *A* and *B*), and in the anteroposterior view (Fig. 34, *A* and *B*) it was noted that both tibiae angulated medially to give a marked tilt to the ankle joints. The cortical thickenings of the fibulae noted at birth had subsided except for their midportions, but with remarkably little bowing of the fibulae compared to that of the tibiae. There was little

Fig. 34. Case VIII. J.P. Age, six months. (*A* and *B*) Anteroposterior views. Marked lateral bowing of the distal thirds of the tibiae.

reactive cortical thickening on the concave surfaces of the bowed tibiae. The femora and the tibiae showed abnormal tubulation with expansion of the subcortical cancellous portions of the shafts.

Fig. 35. Case VIII. J.P. Age, twenty-two months. (*A* and *B*) There is still marked anterior bowing of the tibiae.

Fig. 36. Case IX. D.P. Newborn. Marked subperiosteal cortical thickening of the body and both rami of the mandible and of both clavicles.

Roentgenograms of both legs at the age of twenty-two months (Fig. 35, *A* and *B*) revealed that there was still marked anterior bowing of both tibiae. Since thickening of the cortices was observed on the concave surfaces, the bones appeared to be reacting in accordance with stress.

Case IX. D.P. A daughter of Case VI and a sister of Cases VII and VIII was born at the Porter Hospital, January 19, 1959 after a full term pregnancy terminating with spontaneous delivery. At the time of birth it was noted that the left leg was swollen and the infant appeared unable to move the extremity. Roentgen examination made one hour after delivery showed findings characteristic of infantile cortical hyperostosis in the mandible, clavicles, tibiae, and fibulae (Fig 36 and 37). On February 6,

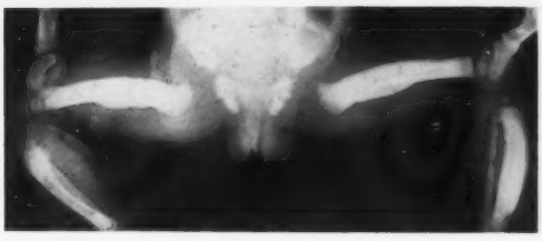

Fig. 37. Case IX. D.P. Newborn. Marked subperiosteal cortical thickening of both femora and tibiae, with slight anterior bowing.

Fig. 38. Case ix. D.P. Age, three months. Regression of the subperiosteal cortical thickening of the mandible.

1959, at the age of two weeks, the patient was transferred to the Mary Fletcher Hospital. Blood cell count showed a mild leukocytosis and a normal hemoglobin. The sedimentation rate was slightly elevated. The alkaline phosphatase was 149 King-Armstrong units. The serum calcium and phosphorus were within normal limits. The urinalysis and blood serology tests were normal.

In view of the severe changes and the poor clinical appearance of the child, it was felt that a course of steroid therapy was indicated. She was placed on cortisone, 50 mg. daily, and discharged two days after admission. Eleven days later she was readmitted with a history of cyanosis and diarrhea. Physical examination revealed a right otitis media. Although the tenderness over the tibiae had decreased, it was thought that cortisone had not altered the course of the disease to any appreciable degree and the drug was discontinued. She was placed on antibiotics and discharged four days later; the otitis media had improved.

Fig. 39. Case ix. D.P. Age, three months. The subperiosteal cortical thickening of the femora has been partially resorbed.

Fig. 40. Case ix. D.P. Age, three months. There is beginning resorption of the subperiosteal cortical thickening of the tibiae.

Fig. 41. Case x. B.B.P. Age, one day. Marked subperiosteal cortical thickening of the mandible.

Roentgenograms taken three months after birth showed distinct regression in the amount of cortical thickening, but definite abnormalities were still present in all bones that previously had been noted to be involved (Fig. 38, 39 and 40).

Case x. B.B.P. Following a full term spontaneous delivery on February 7, 1960, a male infant, brother of Cases vii, viii and ix, was noted to have marked soft tissue swelling of both legs with moderate prominence of the tibiae. The following day, soft tissue swellings of the forearms and over the mandible appeared. The child was generally irritable and fussy and seemed uncomfortable whenever his extremities were moved. He was afebrile throughout his five day hospitalization.

Roentgenograms taken the day after delivery (Fig. 41 and 42) revealed classic hyperostotic changes involving the mandible, clavicles, radii and tibiae.

The infant was examined at six weeks of age, at which time he appeared less irritable. The soft tissue swellings of the extremities appeared to be unchanged and the mandibular swelling was more prominent.

Fig. 42. Case x. B.B.P. Age, one day. Marked subperiosteal cortical thickening of both tibiae and radii.

Fig. 43. Case xi. B.C. Newborn. Subperiosteal cortical thickening of both tibiae.

Case xi. B.C. A female child, a niece of Cases i, ii and iii, was born in the Burlington County Hospital, Mount Holly, New Jersey. At birth she was noted to have soft tissue swellings over the mandible and lower extremities. The child was asymptomatic and did not seem to be in pain. Roentgenographic examination a few hours after birth showed subperiosteal cortical thickening of the mandible, clavicles and tibiae consistent with the diagnosis of infantile cortical hyperostosis. Figure 43 illustrates the subperiosteal cortical thickening of both tibiae.

The child grew and, subsequently, at the age of eleven months, was examined at the deGoesbriand Memorial Hospital. Roentgenograms of the mandible, clavicles, femora and tibiae showed changes consistent with the diagnosis of infantile cortical hyperostosis. There was cortical thickening of the right femur associated with anterior bowing (Fig. 44). Both tibiae showed a marked amount of anterior bowing but no subperiosteal cortical thickening at this time (Fig. 45).

DISCUSSION

The 11 cases reported may be classified as consistent with the diagnosis of infantile cortical hyperostosis. A question might be raised concerning Case vi. At the time of

Fig. 44. Case xi. B.C. Age, eleven months. Subsiding subperiosteal cortical thickening and slight bowing of the right femur.

this report he is twenty-five years of age, the father of 4 typical cases, and a first cousin of 5 other cases. As an infant and in early childhood, he is said to have had painful swelling and deformities of the extremities, which left him with marked bowing of the legs that has persisted into adult life. Unfortunately, he was never examined roentgenographically during the active phase of the disease, but recent roentgen studies show bowing deformities of both femora and tibiae similar in appearance to those reported in certain late stages of infantile cortical hyperostosis. Although no other adult case with changes of this type has come to our attention, Caffey has reported late deformities of a slightly different nature. In view of the above findings it is reasonable to postulate that this patient probably did have infantile cortical hyperostosis in childhood and that a rather unusual type of bony deformity remains.

In the 11 cases reported, there is roentgenologic evidence of the disease having existed in at least two generations of one family. The father of Cases i, ii and iii is said by his family to have had a similar affliction in childhood, but there is no roentgenographic evidence to support this assumption. If this bit of history is reliable, there is evidence that the disease existed in three generations of this one family.

It would appear that the transmission of the disease from the second to the third generation was by the male in one instance and by the female in a second instance. In the possible transmission of the disease from the first to the second generation (for which the family history is the chief source of information), it would appear that the disease was transmitted in 3 instances by the male and in 1 instance by the female. It would, therefore, seem reasonable to conclude that in this family the disease was transmitted by both the male and the female.

It also seems probable from this study that in several cases the disease was transmitted by a parent in whom the disease was not clinically manifest. This could be interpreted as indicating that some individuals may be carriers of the disease without having clinical manifestations or that

Fig. 45. Case xi. B.C. Age, eleven months. Anterior bowing but no subperiosteal cortical thickening of the tibiae.

the disease may be of such a mild nature in some individuals that it is not identified. In support of the latter possibility, it is noteworthy that in our series the manifestations of the disease in Case VIII and Case XI were of a very mild nature with no symptoms of consequence. The disease could easily have been overlooked had it not been for the known history of other cases in the same family.

The evidence presented adds support to the belief expressed previously by Boyes and Demy,[3] Sidbury and Sidbury,[15] Van Zeben[18] and others that this disease has a familial tendency and may be transmitted by the genes, at least in some instances.

The disease is usually self-limiting. Ordinarily, by the end of the first year only a small amount of residual bony deformity remains, and by the third year the bony skeleton has returned to normal in most instances. Cases I, II and III, aged fifteen, thirteen and twelve years, respectively, at the time of this report, are all healthy, well-developed adolescents with no detected traces of skeletal deformities. Case VI demonstrates that the exceptional case (as Caffey also described) may have residual deformities persisting into adult life.

In most respects the roentgen manifestations of the cases presented have followed the usual pattern, both as to the type of involvement of the individual bones and as to the bones involved. It is worthy of note that in the early cases (Case I, II, III, IV and V) the mandibular manifestations of the disease were not as prominent as those usually described.

There is still much to be learned concerning this disease. It is hoped that this presentation will stimulate others to make further inquiries into its familial aspects so that the natural history of the disease may become better understood. Since many of these patients had very mild or atypical symptoms, it is also suggested that roentgenographic studies be made of nonsymptomatic as well as of symptomatic infants in families where the disease has already been manifest.

SUMMARY

1. Eleven cases of infantile cortical hyperostosis in two generations of one family are reported.

2. The cases, added to those already reported by others, lend support to the contention that in some instances this disease has a familial tendency and may be transmitted by the genes of both males and females.

3. In some cases, the clinical and roentgenologic manifestations are marked and severe, while in others they are so mild or atypical that the disease may be easily overlooked.

4. Family histories should be evaluated carefully for all known patients. It is suggested that roentgenographic examinations be carried out on both symptomatic and nonsymptomatic infants in families where the disease has already been manifest.

5. While the disease is usually self-limiting, with no residual deformities, an occasional case may show late skeletal abnormalities persisting even into adult life.

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FAMILIAL IDIOPATHIC OSTEOARTHROPATHY*

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THE term osteoarthropathy (or hypertrophic osteoarthropathy) refers to a well known syndrome manifested principally by clubbing of the fingers and toes, subperiosteal new bone formation and arthropathy. Two major forms of the syndrome are recognized: a secondary and a primary, or idiopathic. The former occurs in the course of, and is precipitated by, an underlying pathologic process; the latter is not associated with any known disease process to which it might be secondary. The idiopathic form is much less common than the secondary, occurring only in approximately 3–5 per cent of cases.[4,20,22] Idiopathic osteoarthropathy has the peculiar tendency to be associated with a special type of pachydermia; when this additional feature is present, the syndrome is often referred to as pachydermoperiostosis. Definite instances of idiopathic osteoarthropathy without pachydermia have been reported.

The major clinical manifestations of the variants of the syndrome, their probable inter-relationships and their relation to simple or primary clubbing will be reviewed briefly. In the case reports, the clinical history and findings of 2 Negro female siblings affected with idiopathic osteoarthropathy without pachydermia will be presented; these 2 children are of interest because of the great rarity of the disease in the first decade of life, and because of some unusual features which they presented in infancy.

SECONDARY OSTEOARTHROPATHY[3,20,22,25,28]

The predisposing lesion, usually of a chronic nature, may be pulmonary, pleural, mediastinal, cardiac, hepatic, or gastrointestinal; on rare occasions it originates in other organs or is systemic. Since in most instances the causative factor is pulmonary, the disease is sometimes also termed pulmonary osteoarthropathy. Males are more commonly affected than females, and adults much more frequently than children.[14] The joint manifestations and the periostitis may be mild or even absent, whereas the clubbing is very seldom, if ever, missing. Joint manifestations occur in approximately one third of the cases and consist of swelling and tenderness, mainly in the knees, ankles and wrists. Joint effusion may be present. Joint pain and pains in the limbs are frequently present, but rarely severe.

Roentgenographically and pathologically there is a symmetric, but usually not very pronounced, periosteal new bone formation, which is often limited to the diaphyses of the long bones (especially the distal portions of the extremities), metatarsals, metacarpals, and proximal and distal phalanges. The new bone tends to have wavy contours and to be separated from the old cortex by a thin radiolucent line. As a rule, the articular surfaces are not disturbed.

The onset of the osteoarthropathy generally follows that of the primary process, but on occasions the osteoarthropathy antedates the onset of the clinical and roentgenographic manifestations of the precipitating lesion even by several months. The symptoms and findings of the osteoarthropathy may wax and wane with the activity of the etiologic process and may clear partially or completely with improvement or cure of the primary disease.

PACHYDERMOPERIOSTOSIS[1,11]

This was first recognized as a separate entity by Touraine *et al.*[31] in 1935. The

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† This paper reflects the authors' personal views and is not to be construed as a statement of official Air Force policy.

affected patients show a marked thickening of the skin of the forehead and face, with prominent creases and folds, suggesting the leonine facies of leprosy. The lids are also thickened. Cutis verticis gyrata* is present in some patients. The clubbing is usually pronounced and the soft tissues of the hands and feet are greatly enlarged. The skin of the distal portions of the forearms and legs tends to be indurated. The skin is oily and the hands and feet show increased perspiration. Joint swelling and articular or limb pain may be present.

Roentgenographically and pathologically all the long bones of the extremities, and in severe cases all the bones of the skeleton, show a symmetric and often severe periosteal new bone formation which, in contrast to that of secondary osteoarthropathy, tends to be confluent with the old cortex. The affected bones are wide and their contours are irregular; their texture is very coarse and their medullary canals are often encroached upon and narrowed. The articular surfaces are usually spared. In the majority of cases the changes start suddenly at fourteen to eighteen years of age and progress for a few years, after which they remain stationary.

The patients are rarely incapacitated and life expectancy does not seem to be affected. The disease affects males almost exclusively and may occur sporadically or in families. A familial incidence has been reported in approximately 25 per cent of the cases. A recessive or irregularly dominant gene has been incriminated.

IDIOPATHIC OSTEOARTHROPATHY WITHOUT PACHYDERMIA

Under this heading may be grouped all the patients with idiopathic osteoarthropathy who do not show any thickening of the soft tissues of the forehead and face. This type of osteoarthropathy is in many other respects similar to, and may be an incomplete form of, pachydermoperiostosis. The disease seems to predominate in males and in the Negro race and can be familial or sporadic. Its manifestations commonly start during the second decade of life. In some patients the clubbing antedates the other features by many years and may even be congenital. Clubbing is apparently always present, whereas the arthropathy or the periostitis may be missing. The periostitis is usually mild and commonly is localized to the long bones of the distal parts of the extremities. The joint swelling may be associated with mild pain. Frequently articular swelling and pain are precipitated or intensified by cold and humid weather. A joint effusion may coexist. In addition to the swelling of the knees, ankles and, often, the wrists, the soft tissues of the hands and feet may show some enlargement, and there may be an induration of the soft tissues of the distal forearms and legs. As in the other forms of osteoarthropathy, increased perspiration of the hands and feet is not uncommon and eczema may be present. General health and life expectancy are not affected.

Probable cases belonging to this category have been described by Berk,[2] Camp and Scanlan,[4] Carruthers,[6] de Sèze and Jurmand,[9] Fairbank,[10] Hollar and Agnor,[15] Keats and Bagnall,[17] Mankowsky *et al.*,[21] Ragins and Freilich,[24] Schönenberg,[26] Thomas,[30] and Weens and Brown.[34] Of interest for their young age are the five and eight year old brothers described by Schönenberg;[26] both had generalized clubbing of the fingers and toes from infancy, chronic eczema, hyperhydrosis of the hands and feet and an increased serum gamma globulin. The younger sibling also had had swelling of the knees since his second year.

SIMPLE OR PRIMARY CLUBBING

Clubbing, which occurs in the various forms of osteoarthropathy, is seen also in cyanotic congenital heart diseases and as a

* Cutis verticis gyrata[23] is an unusual dermatologic condition affecting the scalp and is characterized by the presence of elevated and usually longitudinal skin folds, between which are furrows or grooves resembling brain convolutions. It may involve the whole scalp or only part of it. In 25–50 per cent of the cases, it is present at birth; in the remainder it develops before the end of middle life. It appears to be more common in males and has a familial incidence of approximately 5 per cent. The patients are asymptomatic. There is a primary form which is thought to be a developmental anomaly and a so-called secondary form which follows or accompanies a local or a generalized disease such as that under consideration.

simple or primary anomaly in otherwise normal individuals. The clubbing which occurs in cyanotic congenital heart disease apparently is very seldom associated with periostitis and arthritis[16,32] and may be of a different nature. Simple clubbing[19,35,36] may be sporadic, familial and hereditary. Inheritance is thought to be dominant. The clubbing may be generalized or may involve individual fingers and toes in varying degrees.[22] It may be present at birth but more commonly it becomes evident in childhood or later life. Once present, it does not regress. In some instances, it has become more prominent during middle age.[22] Increased perspiration of the palms and soles is not infrequent. The skin of the distal forearms and legs is sometimes slightly thickened. It has been stated[35] that in simple clubbing there is no tendency toward the development of arthritis or periostitis, but exceptions to this rule can be found in the literature; these exceptional cases have been included in the group of patients considered in the preceding section.

COMMENT

It appears that the various forms of osteoarthropathy, cutis verticis gyrata and simple clubbing are very closely related. This is suggested by the presence of common features, transition forms, and hereditary factors, already mentioned, and by certain observations described in the literature. Patients have been described who, in the course of a disease capable of giving rise to secondary osteoarthropathy, developed a typical pachydermoperiostosis[12,13,18,27] and even a pachydermoperiostosis with cutis verticis gyrata.[7] In at least 1 of these patients, the pachydermia disappeared after the removal of the primary lesions.[27] Secondary and idiopathic osteoarthropathy have been observed in different members of the same family,[9] and a number of patients with either of these entities had relatives affected by simple clubbing or simple cutis verticis gyrata.[8,9,24,29,30,33] As noted previously, patients with congenital primary clubbing may develop an osteoarthropathy in later life.

All these observations, and the fact that the incidence of osteoarthropathy secondary to carcinoma of the lung, bronchiectasis or other diseases is probably higher in families with clubbing osteoarthropathy than in the general population, would suggest that there may be an inheritable or constitutional factor common to all these diseases. This possibility was first raised by de Sèze and Jurmand.[9] Apparently, in all these patients the soft tissues of the tips of the fingers and toes, the periosteum, and the periarticular soft tissues of certain areas react as a physiopathologic unit.

The idiopathic form of osteoarthropathy seemingly manifests itself spontaneously without the need of an excitor, whereas in the secondary type, the presence of a primary pathologic process seems to be necessary to bring out the disease. The mechanism by which the precipitating disease gives rise to the various manifestations of secondary osteoarthropathy is far from certain. A list of the various theories which have been postulated may be found in works by Mendlowitz[22] and Shapiro.[28]

REPORT OF CASES

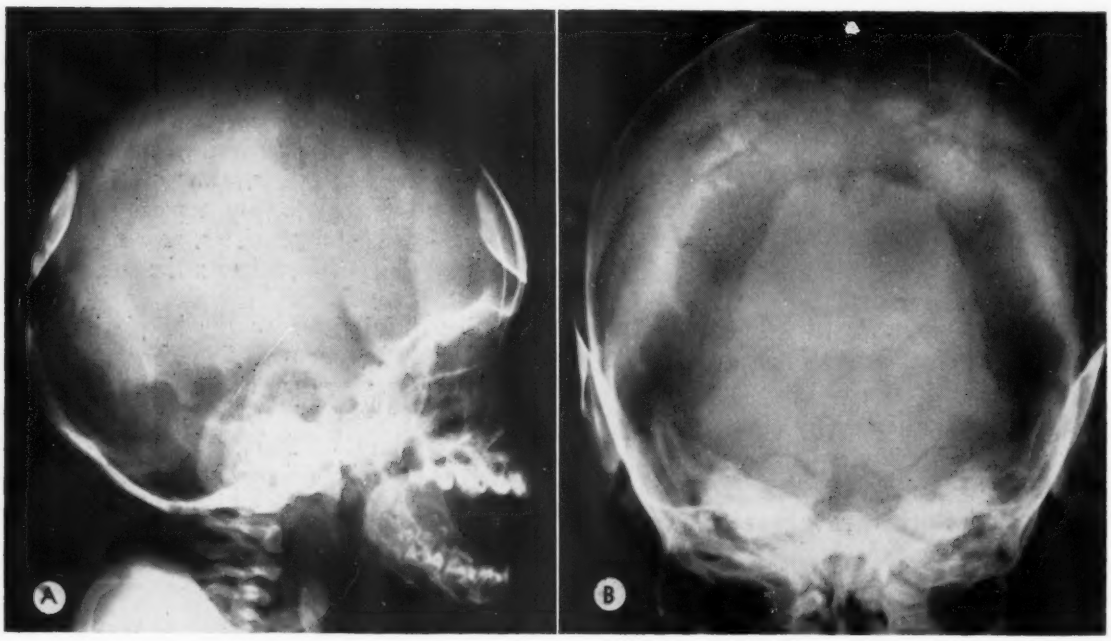
Case 1. B.S., (Fig. 1*A*) a Negro girl now eight years old, has been followed at the Cincinnati General Hospital since infancy. Her parents and three older siblings are living and well and show no clubbing or other abnormalities. Occasionally, however, the mother complains of mild joint pain during cold and humid weather. The skeletal systems of the mother and of an older sister are normal roentgenographically. A younger sister, now six and one half years old, is affected with the same disease (Case 11, Fig. 1*B*).

B.S. was admitted to the hospital for the first time at four months of age for pertussis. It was noted at that time that the fontanels and cranial sutures were extremely wide and that she had a seborrheic dermatitis of the scalp and face. The skin changes had been present for approximately one month and the findings in the skull had been present since birth. The head was otherwise normal in size and shape and there was no evidence of increased intracranial pressure. A roentgenographic examination of the chest and of the entire skeletal system

FIG. 1. (*A*) Case I at eight years of age and (*B*) Case II at six and one half years of age. Note swelling of knees, ankles, and wrists, clubbing of the fingers and toes, and small areas of hyperpigmentation of the skin, especially in the legs.

showed nothing unusual except for the presence of very wide cranial sutures and fontanels (Fig. 2, *A* and *B*). At seven months, her fingers were noted to be clubbed. During her ninth month she developed a generalized eczema for which she was again hospitalized. History at that time revealed that she had had an adequate but not excessive intake of vitamins. In addition to the widely patent cranial sutures and obvious clubbing of the fingers and toes, there were weeping, infected, eczematoid lesions most marked on the face, forehead, scalp and ears. The skin over both pretibial areas was indurated and tender. The rest of the physical examination was not remarkable. Roentgenograms of the chest again showed normal lungs, heart, and mediastinum. The roentgenograms

FIG. 2. Case I. (*A* and *B*) Roentgenograms of the skull taken at the age of four months showing marked widening of sutures and fontanels secondary to delayed bone formation along the margins of the calvarial bones. Note also sutural bones.



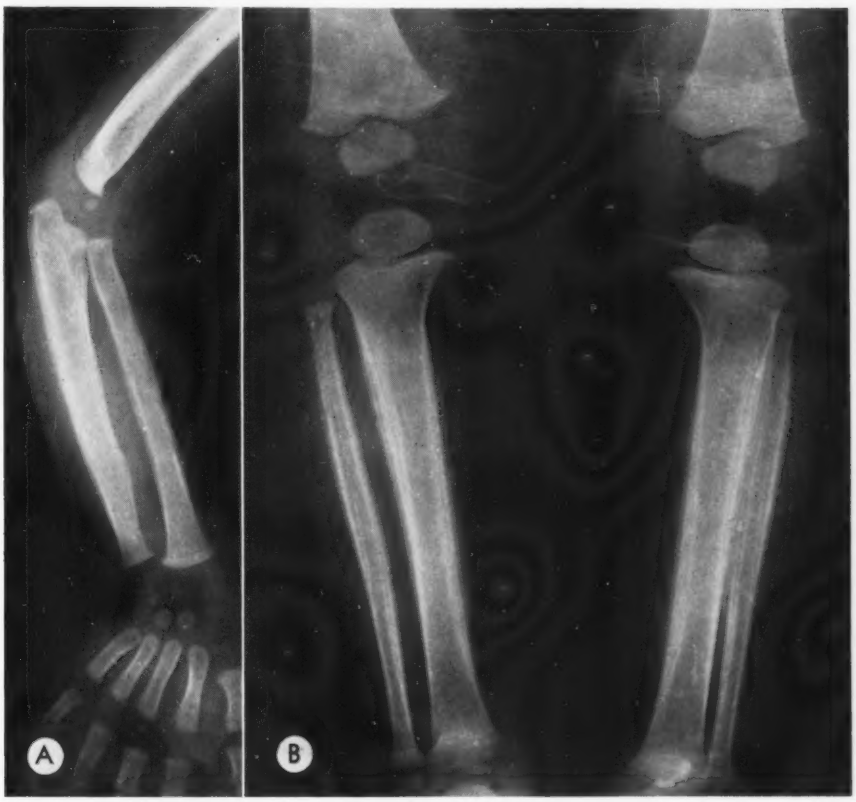


Fig. 3. Case 1. (*A* and *B*) Long bones of the extremities at the age of nine and one half months showing a diffuse periosteal new bone formation. The same bones were entirely normal roentgenographically five and one half months previously.

of the skeletal system revealed considerable subperiosteal new bone formation in the shafts of all the long bones (Fig. 3, *A* and *B*). A minimal periosteal reaction was also present in the clavicles. The sagittal and lambdoid sutures were still very wide and contained small sutural bones. The mandible was normal. At nineteen months of age, she was admitted to the hospital for diarrhea and again for bronchitis, bilateral otitis media and an exacerbation of the eczema. Following discharge from the hospital she did well until the age of two years, when she developed a diffuse swelling of both knees. A physical examination at that time showed that both knees were swollen but not tender. Seborrhea was present on the scalp, and a lichenified, scaling dermatitis involved the back, buttocks, abdomen and antecubital and popliteal regions. Roentgenographically, the fontanels and cranial sutures appeared narrower than previously, but large unossified areas still remained in both limbs of the lambdoid suture (Fig. 4). Evidently, most of the improvement

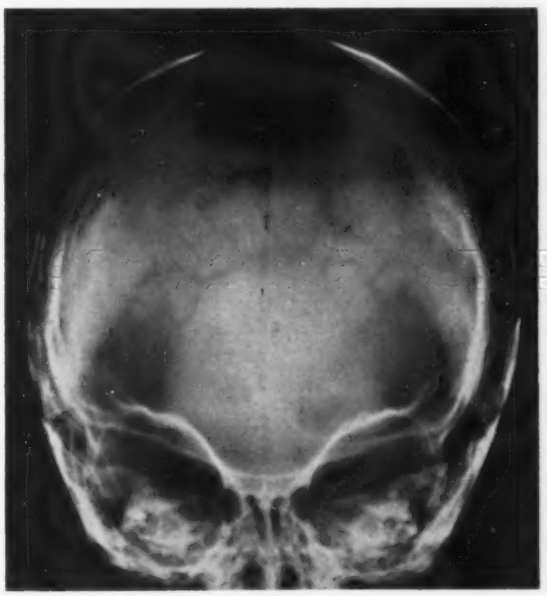


Fig. 4. Case 1. Roentgenogram of the skull at the age of two years showing residual widening of the cranial sutures and large sutural bones.

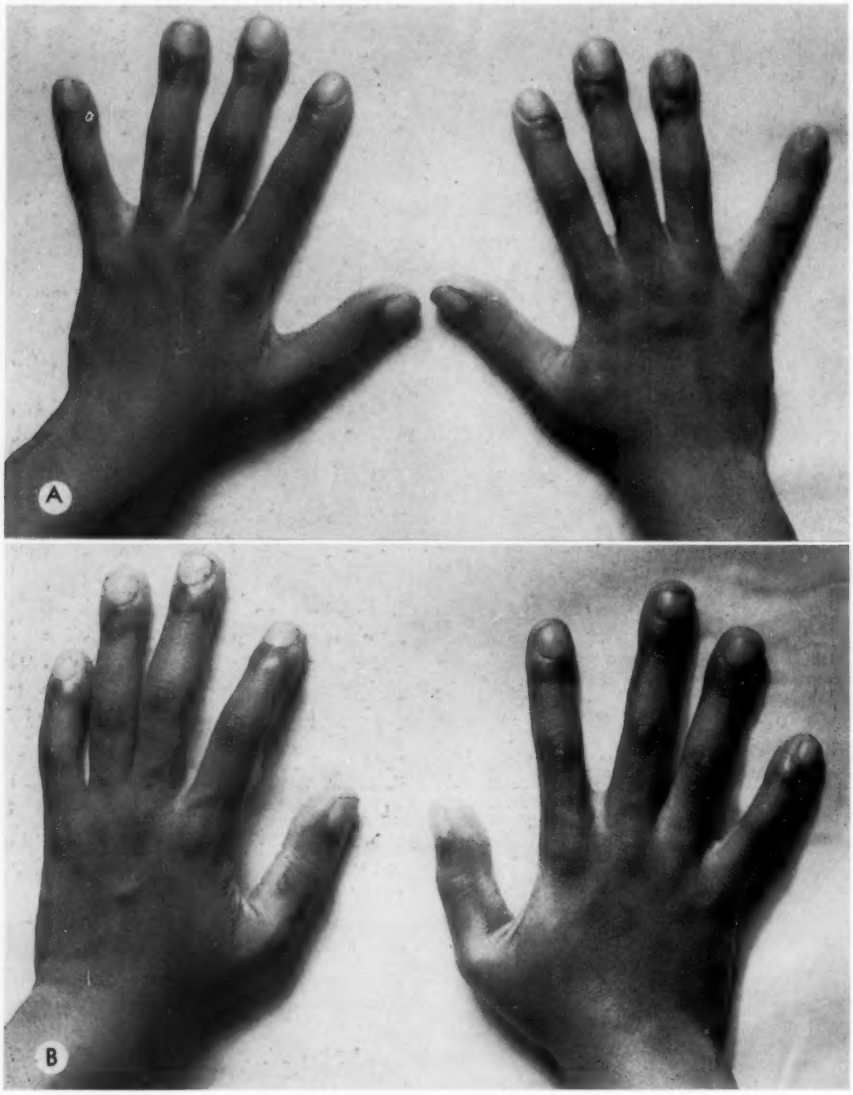


FIG. 5. (*A*) Hands of Case I at the age of eight years and (*B*) hands of Case II at the age of six and one half years. Note clubbing of the fingers.

in the roentgen appearance of the skull was due to an increase in the size of the sutural bones. The roentgenograms of the rest of the skeletal system showed no residual periosteal reaction except for a small amount in the central portion of each ulna. However, the diaphyses of all the long bones of the extremities were wider than normal and their cortices were thickened, suggesting that the previously seen subperiosteal new bone had become fused with the old cortex. A biopsy of the central portion of the right tibia revealed normal skin, subcutaneous tissue, muscles and bone; the periosteum showed a proliferating reaction, without inflammation. At thirty-three months, the anterior fontanel measured 3×3 cm., while the posterior fontanel was barely patent. The eczema was clearing. During the ensuing years, the fontanels and cranial sutures closed gradually but the swelling of the knees remained stationary. Between her fourth and eighth year she suffered several bouts of pain, tenderness and increased swelling of both knees, lasting two or three days. These attacks took place mainly during inclement weather and, usually, were heralded by a respiratory infection and accompanied by a low grade fever. In the interval she was asymptomatic.

Fig. 6. Case 1. (*A*, *B* and *C*) Long bones of the extremities at the age of eight years. Normal long bones except for minimal periosteal new bone formation in the distal third of the ulna, which was probably of recent onset.

The last admission to the hospital, at the age of eight years, was precipitated by one of these attacks with involvement of both knees and, for the first time, also the ankles. All her somatic measurements were between the tenth and twenty-fifth percentile, and her mental development was normal. The degree of clubbing present at that time is illustrated in Figure 5*A*. The skin showed no residual eczema, but areas of hyperpigmentation were present, especially on the legs. The soft tissues of the pretibial regions were slightly indurated. The knees and ankles were swollen and moderately tender. A small effusion was detectable in both knee joints. The palms and soles exhibited a distinct hyperhydrosis. Roentgenograms of the skull (Fig. 7), chest and long bones showed no abnormalities, except for a minimal subperiosteal new bone formation in the distal third of

Fig. 7. Case 1. Lateral view of the skull at the age of eight years showing no unusual finding.

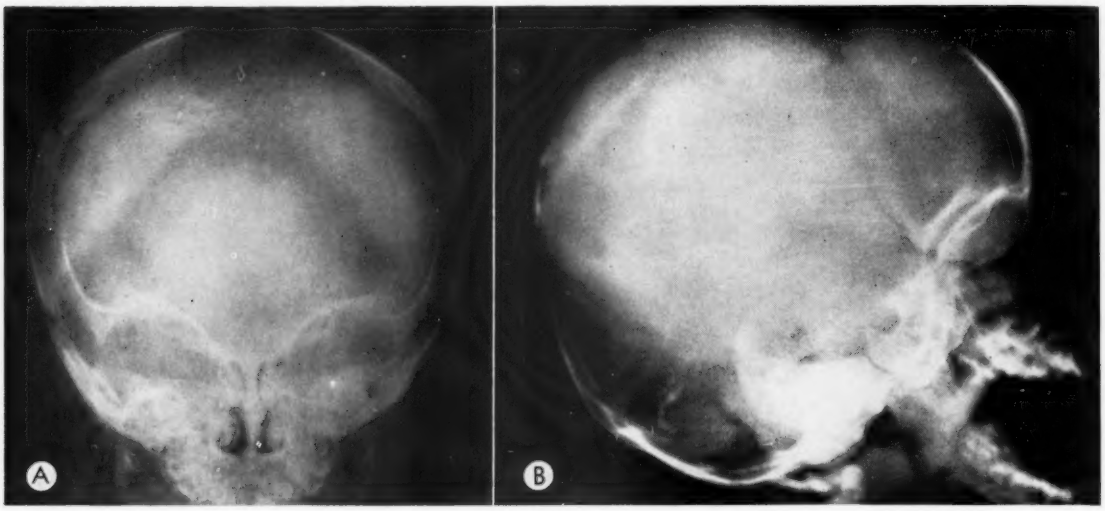


FIG. 8. Case II. (*A* and *B*) Roentgenograms of the skull at the age of seven months. Note widening of the cranial sutures and sutural bones.

each ulna, laterally (Fig. 6, *A–C*). All the long bones, including those of the knees and ankles, were normally tubulated and had normal contours, texture and mineral content. Aspiration of the knee joints yielded approximately 15 cc. of fluid. The fluid from the left knee was blood tinged and contained 3,350 white blood cells and 240,000 red blood cells/cu. mm. The fluid from the right knee was thick and yellow and contained 14,000 white blood cells/cu. mm. with 64 per cent mononuclear and 36 per cent polymorphonuclear cells. The protein content of the fluid obtained from both knee joints was 2,900 and the sugar content was 90–100 mg. per cent. Both fluids were sterile. A synovial biopsy revealed microscopic evidence of chronic synovitis.

Multiple other clinical and laboratory investigations were performed during the various hospitalizations. Repeated tuberculin and histoplasmin skin tests, Kahn reactions, electrocardiograms, sickle cell preparations and urinalyses always gave negative results. The hemoglobin and red blood cell count were constantly slightly decreased. The platelets, white blood cells, and differential distribution of the white blood cells were always within normal limits, except for a leukocytosis of 20,000 per cu. mm., with a lymphocytosis of 70 per cent, during the first two admissions. A bone marrow smear at the age of ten months showed no abnormalities. The blood urea nitrogen, creatinine, uric acid, calcium, phosphorus, alkaline phosphatase, total proteins, albumin, bilirubin, carotinoids, vitamin A, total lipids and cholesterol never showed any significant variation from normal values, except for an alkaline phosphatase of 30 Bodansky units at nineteen months of age, which was again normal a month later. Throughout the period of observation, the corrected sedimentation rate (Wintrobe) always ranged between 31 and 36 mm. in one hour. The zinc sulfate turbidity was consistently increased. The thymol turbidity and cephalin-cholesterol flocculation were increased in the first two admissions but negative subsequently. The total serum globulins, in the various hospital admissions, ranged between 3.4 and 4.3 mg. per cent, with a gamma fraction ranging between 1.4 and 1.93 mg. per cent. Several L.E. preparations, an ASO titer determination, and a latex fixation test during the last admission were normal.

CASE II. J.S., (Fig. 1*B*) sister of Case I, was admitted for the first time to the Cincinnati General Hospital at the age of seven months for eczema, of six weeks' duration, and an apparently painful swelling of the extremities, of three weeks' duration. A clubbing of the fingers and toes was first noticed two weeks prior to admission. Her height, weight, and head circumference were within normal limits. The fontanels and all the cranial sutures were abnormally wide. No signs of increased intracranial pressure could be detected. A scaling eczematoid dermatitis was present over most of her body but was most marked in the diaper

areas; the scalp was not involved. The soft tissues of the forearms and legs were thickened but showed no pitting or tenderness. The remainder of the physical examination was not contributory. The tuberculin and histoplasmin skin tests and the Kahn reaction were negative. A urinalysis revealed a trace of albumin and an occasional white blood cell. The hemoglobin was 12 gm. per cent. The white blood cell count

Fig. 9. Case 11. (*A*, *B* and *C*) Long bones of the extremities at the age of seven months showing diffuse periosteal new bone formation.

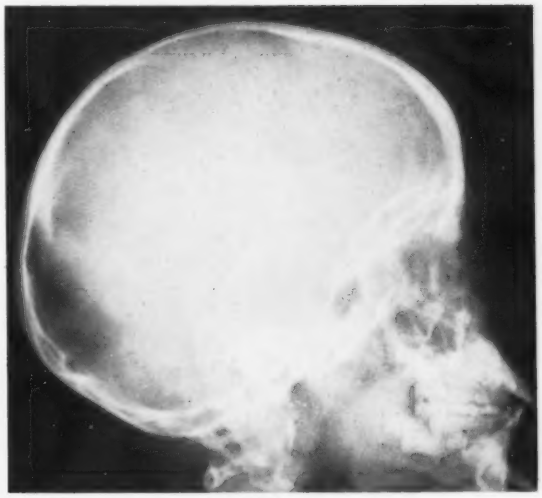


Fig. 10. Case 11. Roentgenogram of the skull at the age of six and one half years showing no abnormalities except for a residual oval bony defect in the left limb of the lambdoid suture.

was 9,500 per cu. mm., with a normal differential distribution. The hematocrit was 33 per cent. The corrected sedimentation rate (Wintrobe) was 26 mm. in one hour. The electrocardiogram was normal. The serum calcium, phosphorus, and alkaline phosphatase were within normal range. The serum vitamin C content was 0.3 mg. per cent fasting and 0.6 mg. per cent four hours after an intramuscular injection of 200 mg. of ascorbic acid. The roentgenograms of the skull showed a severe widening of the sutures and fontanels and the presence of many sutural bones, posteriorly (Fig. 8, *A* and *B*). The shafts of all the long bones of the extremities showed a considerable amount of subperiosteal new bone formation (Fig. 9, *A–C*). A mild periosteal reaction was also present in the clavicles. The rest of the skeletal system, and in particular the mandible, was not unusual. The heart and lungs were normal roentgenographically and fluoroscopically. Following discharge from the hospital, the dermatitis and the swelling of the extremities regressed gradually. At thirteen months of age the dermatitis was found to be limited to a small area on the right thigh. At that time, the cranial sutures and fontanels were still abnormally wide and the clubbing was even more conspicuous than previously.

At the age of four and one half years, she was brought to the outpatient department of the hospital because of fever and joint pain and swelling of a few days' duration; these symp-

FIG. 11. Case II. (*A*, *B* and *C*) Long bones of the extremities at the age of six and one half years. The bones are well tubulated and mineralized and show no residual periosteal new bone formation.

toms had appeared seven days after a booster injection of diptheria-pertussis-tetanus antigens. Her mental and physical development was normal. The fontanels and cranial sutures were no longer patent. A nontender effusion was present in both knee joints and the pretibial area and the feet were swollen.

In the ensuing two years, the patient gradually developed a mild chronic swelling of the periarticular soft tissues of the knees and ankles, and she suffered recurrent episodes characterized by pain and further swelling in these joints. The attacks were identical in all respects to those described in the sister. Between attacks the child was entirely asymptomatic. A reexamination at six and one half years of age showed that the positive physical findings were limited to the extremities. The fingers (Fig. 5*B*) and toes showed a definite clubbing, and the periarticular soft tissues of the knees and ankles were mildly swollen. The palms and soles exhibited increased perspiration. The skin showed small areas of hyperpigmentation, especially in the legs. Roentgenographically, the skull was normal, except for a small oval radiolucent defect in the left limb of the lambdoid suture (Fig. 10). The heart, lungs, and pleural spaces were normal, as were the long bones of the extremities (Fig. 11, *A–C*), the thoracic cage, pelvis, and spine. The tufts of the distal phalanges of the hands were well formed, whereas those of the distal phalanges of the feet were small and pointed as in the sister.

DISCUSSION

The clinical history and findings of the 2 siblings reported in this paper were prac-

tically identical. Both patients showed congenital enlargement and delayed closure of the cranial sutures and fontanels, a bout of severe subperiosteal new bone formation involving the diaphyses of the long bones of the extremities, and to a lesser degree the clavicles, lasting throughout the second half of the first year of life and the entire second year, an eczematoid dermatitis coincident with the periosteal reaction, clubbing of the fingers and toes, which became apparent during the sixth month of life, and a chronic swelling of the knees, and later also of the ankles, which started between the second and fifth year and which was soon followed by recurrent attacks of pain and increased swelling in these joints.

There is probably little doubt that the over-all clinical picture presented by these 2 patients was that of familial idiopathic osteoarthropathy without pachydermia. Unusual features in both instances were the bouts of periosteal reaction and simultaneous eczema in early life, and the congenital developmental changes in the skull. A review of the material in the available literature on clubbing osteoarthropathy has failed to reveal any patient in whom findings in early life identical to these were described. A full explanation for these features cannot be given at the present time, but the possibility is suggested that they were early manifestations of the trait of the clubbing osteoarthropathy syndrome, which in both instances did not become obvious until later.

The simultaneous occurrence of eczema and hyperostosis probably indicates that these two features were related, but whether they developed independently (spontaneously or as a result of some unknown noxa), or whether the eczema precipitated the bone changes is not known. As mentioned previously, eczema is not uncommon in, and may be a manifestation of, the syndrome of osteoarthropathy.

As regards the skull changes, the possibility that they too were part of the disease derives some support from the appearance of the skull roentgenograms of the 2 brothers reported by Schönenberg.[26] The reproductions of these skull roentgenograms present features which strongly suggest a delayed mineralization of the cranial sutures and fontanels and which show multiple sutural bones not unlike those described in our patients.

If future observations will confirm these assumptions, then idiopathic osteoarthropathy will have to be considered as an additional, although rare, cause for congenital widening and delayed closure of cranial sutures and fontanels, and for cortical hyperostosis in infancy and early childhood.

SUMMARY

The subject of osteoarthropathy is briefly reviewed and case histories of 2 female Negro children (siblings) affected by idiopathic osteoarthropathy are presented.

In addition to the usual features of the disease, both patients showed marked congenital enlargement and delayed closure of the cranial sutures, and had bouts of severe periostitis and eczema in infancy and early childhood.

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HYPERCALLOSIS IN OSTEOGENESIS IMPERFECTA*

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THE multiple fractures present in cases of osteogenesis imperfecta heal as a rule with normal formation and resorption of callus in spite of the known deficiency of subperiosteal osteoblasts in this condition. The occasional development of massive callus in these patients cannot be satisfactorily explained. Excessive reaction of bone sometimes occurs with formation of material consisting of fibromucoid tissue first and hypercellular bony trabeculae later. The histologic picture may be mistaken for that found in osteogenic sarcoma, and has been thoroughly described by Baker.[2]

Few cases are found in the literature after the original case reported by Battle and Shattock[3] in 1908. Nevertheless, it is important to recognize this condition as it has been frequently mistaken for malignancy. Several patients reported have been subjected to radiation therapy or amputation following a diagnosis of sarcoma, although it is known that the occurrence of a true neoplasm on a fracture site is very rare,[2] and only a few cases of sarcoma occurring in osteogenesis imperfecta are found in the literature.[6,7]

CLINICAL AND ROENTGEN FEATURES

Exuberant formation of callus can occur spontaneously, following minimal trauma or after a fracture in a patient known to suffer from osteogenesis imperfecta. The femur is commonly affected and a firm mass develops accompanied by local heat, tenderness and redness. Fever, leukocytosis and elevation of the sedimentation rate can occur while callus is forming in the early phase of this condition. The fever and local signs observed in these cases suggest, at times, the presence of an osteomyelitic process.[1] The blood chemistries reveal normal values of calcium and phosphorus, and the alkaline phosphatase can sometimes be elevated due to the presence of recent fractures.

A classic history of osteogenesis imperfecta of the so-called postnatal, nonfamilial type is obtained from these patients. Deformities of the limbs are commonly found and blue sclerae may be present.

A large amount of callus formation can be detected roentgenographically soon after the discovery of the swelling of the affected limb, or four to six weeks after a fracture is sustained. Rapid growth of callus ensues and a large osseous mass can then be seen expanding in all directions and bulging out on one or both sides of the shaft of the bone. The dense, sometimes structureless mass tends to comprise a large portion of the affected shaft, simulating the roentgen features of osteogenic sarcoma (Fig. 1, *A* and *B*).

A common finding in these patients is the presence of bony excrescences along the shafts of the long bones resembling exostoses (Fig. 2). These are said to occur in about 50 per cent of cases.[9] Fine spicules can also be seen, particularly at the shafts of the radius and ulna at the level of the interosseous borders. These may occasionally fuse, producing synostosis between the two bones.[4]

A peculiar type of deformity of the elbow with dislocation of the radial head may also be noted (Fig. 3), as well as general osteoporosis and other roentgen features typical of osteogenesis imperfecta.

The large osseous mass sometimes remains unchanged for a long period of time, but not infrequently it regresses slowly and eventually may disappear without any specific treatment.

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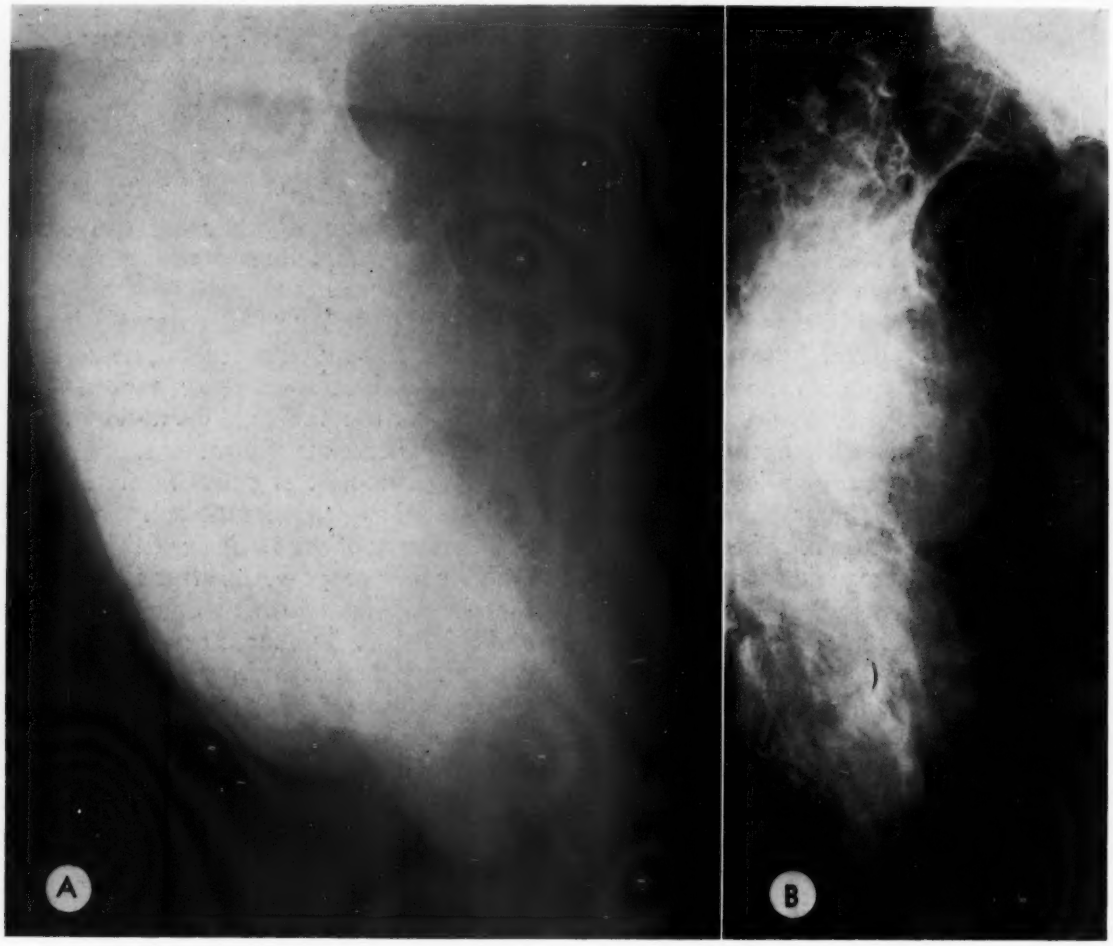

Fig. 1. (*A*) A large osseous mass is seen involving most of the shaft of the right femur of an eighteen year old boy with osteogenesis imperfecta. Numerous fractures sustained in other areas since birth have healed in a normal fashion. No recent history of trauma was obtained. (*B*) The reticular appearance of the bony mass can be seen in this roentgenogram. A presumptive diagnosis of osteosarcoma was made. Biopsy revealed changes consistent with abnormal repair of callus.

DISCUSSION

Fontaine and his co-workers[5] believe that the hypercallosis is due to bone metaplasia originating at the site of trauma from local hemorrhage, with blood transforming into osseous material. The presence of the bony excrescences is explained by these authors as the result of localized detachment of the periosteum by small hematomas, with subsequent bone formation. Nevertheless, excessive local hemorrhage and subperiosteal hematomas have not been found in biopsies taken in these cases; and in some instances the hypercallosis occurs spontaneously without preceding injury.

Although there seems to be a definite relationship between hypercallosis and osteogenesis imperfecta, the exact nature of the condition has not been clarified. The presence of hypercalcemia in the early stage of this condition has been recently reported in one case,[5] and was thought to be a significant feature worthy of further research studies. Although an unusual finding for patients with osteogenesis imperfecta, the presence of hypercalcemia could not account for simultaneous fractures occurring at other sites and healing in a normal

FIG. 2. Roentgenogram of the left femur of the same patient shown in Figure 1. Several excrescences along the shaft are noted; these were also present in other long bones.

FIG. 3. Roentgenogram of the left forearm demonstrates the dislocation of the radial head. This deformity was present in the opposite elbow and represents a common finding in patients with hypercallosis.

fashion without excessive formation of callus.[8]

It seems that a tendency to compensate in volume for the poor osteoblastic function and the faulty quality of the bones by massive callus formation exists in these patients. The deformity of the elbow, occurring in about 25 per cent of cases, could be explained as due to shortening and bowing of the ulna, producing dislocation of the radial head. It is puzzling to see this type of deformity in patients with hypercallosis and not in other cases of osteogenesis imperfecta.

SUMMARY

Hyperplastic, massive formation of callus can occur in cases of osteogenesis imperfecta and may be mistaken for malignancy. The clinical, histologic and roentgenographic features of this condition are difficult to differentiate from those occurring in sarcoma, but its recognition is important in order to avoid surgical intervention. The presence of a large osseous mass at the shaft of a long bone of a patient with osteogenesis imperfecta should be suggestive of hypercallosis. Other common features found in these cases are: peculiar deformity of the elbows with dislocation of the radial head, and multiple osseous excrescences at the shafts of the long bones. The nature of this rare process has not yet been clarified.

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SKULL CHANGES IN CHRONIC IRON DEFICIENCY ANEMIA*

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CHARACTERISTIC changes in the skull have long been recognized in the congenital hemolytic anemias in infancy and childhood. In these disorders there is increased proliferation of hemopoietic tissue in the skull with resultant widening of the diploic space. The outer table is displaced externally and is often thinned. In some cases it is completely atrophied. Occasionally the diploic trabeculae assume a position perpendicular to the inner table presenting a radial pattern which, when advanced, is referred to as a hair-standing-on-end appearance. Caffey[2] has pointed out the usual absence of involvement of the occipital squamosa inferior to the internal occipital protuberance.

In 1958 Lie-Injo,[5] reporting from Djakarta, described similar changes in a twelve year old Indonesian girl with chronic iron deficiency anemia. More recently Shahidi and Diamond[6] have reported identical changes in the skulls of 3 white infants, 2 of them twins, all of whom suffered from iron deficiency anemia. Their patients were eight and twelve months of age.

The purpose of this communication is to describe skull findings, similar to those considered characteristic of the congenital hemolytic anemias, occurring in a three year old Puerto Rican male with chronic iron deficiency anemia.

REPORT OF A CASE

This was the third admission of a three year old Puerto Rican male who was hospitalized for further evaluation of a possible Sturge-Weber syndrome.

The child had been born at term at another hospital after a normal pregnancy and delivery. At birth he was found to have diffuse port wine staining over the scalp, face, upper trunk, lower back and both lower extremities. At the age of one and one-half months he developed right sided Jacksonian seizures. His first two hospitalizations (one and one-half and three months of age) were diagnostically inconclusive despite numerous laboratory studies and procedures including pneumoencephalography, electroencephalography, cerebral arteriography and spinal taps. It was felt, however, that the findings were not inconsistent with the Sturge-Weber syndrome or some other cerebral vascular defect. Between the second and third admissions the patient was observed periodically in the outpatient department. His convulsions were partially controlled with dilantin and phenobarbital but there was marked mental retardation. He could not sit up or stand and he did not talk. He would not take any solid or semi-solid foods, his diet consisting almost exclusively of milk.

On this admission the child was found to be poorly developed, although fairly well nourished. The eyes did not follow light and the pupils did not respond to light. The sclerae showed a bluish-black discoloration. The fundi were not visualized. The port wine stain was again noted extending over a large portion of the head, trunk and extremities. The abdomen was soft and scaphoid, and the liver was palpable 3 cm. below the costal margin. The head was large with prominent bossing of the frontal, parietal and occipital bones.

Repeated blood studies showed hemoglobins of 6.1, 7.5, 7.2, 7.0 and 6.1 gm. per cent. There was marked hypochromia. The red blood cells were microcytic. Coombs' and sickling tests were negative. Hemoglobin study showed only A hemoglobin. There was only an insignificant trace of fetal hemoglobin. Alkaline phosphatase was 11.1 King-Armstrong units; calcium 9.3 mg. per cent; phosphorus 4.8 mg. per cent. Sternal marrow aspiration showed a marked erythroid hyperplasia. No iron could be demonstrated in the marrow.

A skeletal roentgen survey showed some de-

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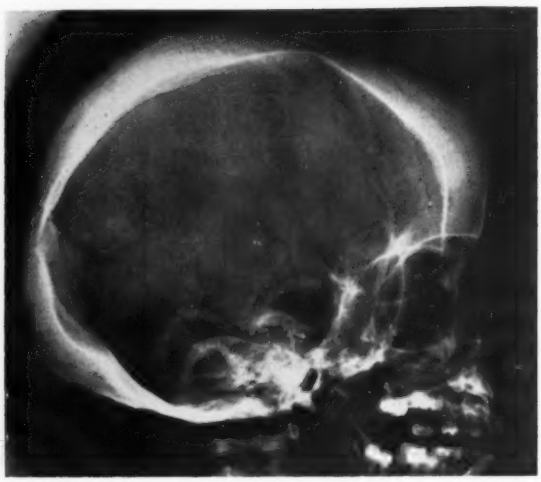

Fig. 1. Lateral roentgenogram of the skull at the age of three years. The diploic space is widened and the parietal trabeculae show a fine radial pattern. The outer table is atrophic and there is a generalized granular osteoporosis. The inferior segment of the occipital squamosa is free from involvement, probably because there is normally no marrow in this portion of the bone.

mineralization of the bones of the extremities consistent with osteoporosis due to relative disuse and to hypervascularity related to the hemangiomata. The cortices of the short tubular bones of the hands were thinned but there was no loss of normal contours of these bones. In the skull there was marked widening of the diploic space in the frontal, parietal and occipital bones with tapering at the edges (Fig. 1). In the parietal bone the diploic trabeculae showed a fine radial pattern perpendicular to the inner table. Roentgenograms made in the outpatient department one and a half years previously had shown similar changes but without any tendency to radial striation of the trabeculae (Fig. 2). Skull roentgenograms made on the first two admissions were reviewed. Those made at the age of three months as part of a pneumoencephalographic study showed early widening of the diploic space in the frontal bone (Fig. 3). At that time there were no abnormalities of the bones of the extremities.

After a review of the clinical and laboratory findings, the diagnosis of Sturge-Weber syndrome and iron deficiency anemia was made. The patient was put on iron therpy (imferon) and showed a definite reticulocytic response and an increasing hemoglobin level when discharged from the hospital.

Fig. 2. Lateral roentgenogram of the skull made at the age of twenty months. There is marked widening of the diploic space in the frontal, parietal and occipital bones. The widening is at the expense of the outer table which is displaced externally and is atrophic. The generalized diploic widening does not involve the inferior segment of the occipital squamosa below the internal occipital protuberance.

DISCUSSION

The presence of an iron deficiency anemia in this three year old child was indicated by the prompt response of the hypochromic microcytic anemia to iron therapy. Hemoglobin studies showed no pathologic hemoglobin and only an insignificant trace of

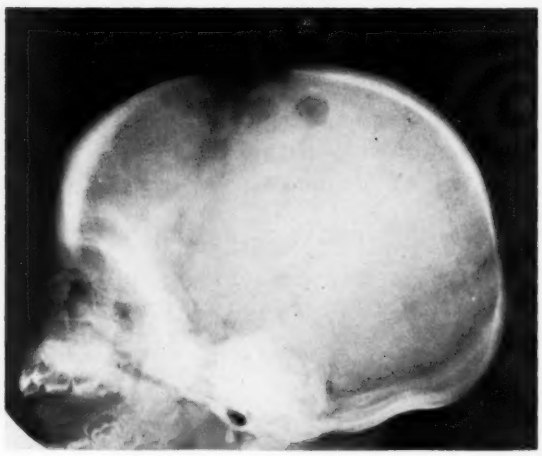

Fig. 3. The skull at the age of three months shows early widening of the diploic space in the frontal bone.

fetal hemoglobin. No iron was found in the sternal marrow, which was hyperplastic.

It is considered that the iron deficiency resulted from a diet which consisted almost exclusively of milk. The 3 cases reported by Shahidi and Diamond[6] also suffered from a consistently poor intake of solids and semisolids and the diets consisted mainly of milk. In the twelve year old Indonesian patient reported by Lie-Injo,[5] the iron deficiency anemia was believed to have resulted from chronic loss of blood from the intestinal tract due to hookworm infestation. The child's diet was considered to have been adequate.

Skull changes similar to those occurring in the congenital hemolytic anemias have also been reported in other conditions accompanied by erythroid hyperplasia. Ascenzi and Marinozzi[1] described such skull findings in 2 girls, aged three and one-half and six years, with cyanotic congenital heart disease and secondary polycythemia. In the three and one-half year old child the cardiac malformation was that of pulmonary atresia with an interatrial septal defect. In the six year old girl there was a tetralogy of Fallot. At autopsy both skulls showed marked erythroid hyperplasia of the marrow with widening of the diploic space similar to that seen in Cooley's anemia, sickle cell disease and familial hemolytic icterus. Erythroid hyperplasia in cyanotic congenital heart disease is due to the hypoxemia resulting from the circulatory shunts. Dykstra and Halbertsma[3] have reported skull changes of the same kind in a twelve year old patient with polycythemia vera.

The skull changes found at the age of three months in this patient represent the first such changes to have been described at such an early age. It is noteworthy that at this age there were no long bone changes that were considered significant. Of the 4 previously reported cases of skull changes in iron deficiency anemia, none showed any abnormality of the bones of the extremities.

In Cooley's anemia, on the other hand, the marrow changes tend to be more conspicuous and are more consistently found in the long and short tubular bones, particularly in the metacarpals and distal femora. Changes are often manifest in the extremities when none are present in the skull but we have not seen skull changes in the absence of tubular bone alterations in infants and young children. After puberty, when the lesions in the tubular bones regress, involvement of the central skeletal segments, as well as the skull, may persist and increase.

We are not able to interpret with certainty the significance of the changes in the hands of this three year old child because of the vascular abnormality involving the regional soft tissues. Holt,[4] however, states that he has seen a case of iron deficiency anemia with long bone as well as skull changes. Shahidi and Diamond,[6] commenting on the absence of long bone changes in their patients, suggest that by the time iron deficiency anemia appears in the infant the cortices of the long bones are firm enough to resist marrow expansion. Those of the cranium offer no resistance.

Whatever the responsible factors may be, the few recorded cases of skull changes in iron deficiency anemia appear to differ from Cooley's anemia in that they show remarkable skull changes without any significant alterations of the tubular bones. Larger numbers of cases of iron deficiency anemia will have to be studied, however, before this difference can be considered a general rule.

SUMMARY

Skull changes similar to those characteristic of the congenital hemolytic anemias are described in a three year old male child with iron deficiency anemia. The earliest changes were demonstrable at the age of three months.

In this condition skull changes appear to occur in the absence of any significant long bone alterations. This is unlike the findings in Cooley's anemia, in which lesions of the long and short tubular bones always accompany skull changes in infants and young children.

Attention is called to the fact that identical skull changes have been reported in cyanotic congenital heart disease and in polycythemia vera.

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THE LATERAL CRANIAL SILHOUETTE IN MONGOLISM*

By F. S. SEWARD, A. F. ROCHE, *and* S. SUNDERLAND
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SOME clinicians regard posterior flattening of the head to be helpful in confirming the diagnosis of mongolism. This investigation was undertaken because the literature reveals frequent repetition of such opinions without attempts to evaluate their accuracy and because descriptions of the shape of the anterior portion of the cranium differ widely.

REVIEW OF THE LITERATURE

The forehead in mongolism has been described as normal (Greig[8]), normal except for prominent frontal eminences (Brousseau[5]), flattened anteroposteriorly (Sutherland[15]), square (Talbot[16]), high at the age of one year (Benda[2]), and with "the lower part of the fore-head . . . on a plane posterior to that of the upper" (Muir[10]).

Opinions concerning the form of the posterior portion of the cranium also vary. Some describe constant marked flattening (Shuttleworth,[12] Talbot,[16] Brousseau,[5] Gosman[7]), but Still[13] has made a less definite statement that "the occipital region tends to be flattened, so that the back of the head loses its rounded contour." Levinson, Friedman and Stamps[9] reported posterior flattening in 41 of 50 cases while Benda[2] stated that it was usually present at the age of one year.

Other reports, however, (Muir,[10] Sutherland,[14] Garrod and Langmead[6] and *The British Medical Journal*[3]) make it clear that such flattening may be absent, while Greig[8] reported that no posterior flattening was present in the 3 skulls he described. He concluded that "it seems as if the differences made by the soft parts had been underestimated, and if the filling up by the nuchal muscles and the fleshiness over the zygomata had not been appreciated." In fact, Greig reported that in one skull "the posterior segment seems disproportionately capacious."

MATERIAL AND METHODS

Although attempts have been made to position mongoloid children in a Bolton-Broadbent cephalometer (Broadbent[4]), difficulties are associated with their management and only a few roentgenograms were suitable for metric analysis. The lateral silhouette has been measured in standardized roentgenograms of 11 boys (ranging in age from two years to five years) and in those of 11 adult males and 11 adult females.

Because of the small number of roentgenograms, it was considered desirable to measure the form of the cranium as a whole rather than the form of its component bones. This decision was prompted by the finding of Pearson and Davin[11] that "the variability of the skull as a whole is less than that of its component bones."

On each tracing of a roentgenogram, a perpendicular to the Frankfort horizontal plane was drawn through basion. The midpoint of this perpendicular was called "C" and radii were drawn from this point to the external cranial margin. The first radius was drawn parallel to the Frankfort horizontal plane and succeeding measurements were taken along radii at angles of 30° to the preceding one (Fig. 1). All measurements along the radii have been expressed as percentages of the cranial height through basion to allow direct comparison between the shapes of skulls of different sizes. In addition, the maximum cranial length was recorded parallel, and

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TABLE I

MEANS AND STANDARD DEVIATIONS FOR THE MEASUREMENTS ON CEPHALOMETRIC ROENTGENOGRAMS
(5+ means "round up" and 5− means "round down")

	Anterior Radii				Posterior Radii				Height	Length
	C-Na	0	1	2	5	6	7	8		
NA ♂	66.47	66.01	59.59	52.17	58.14	65.64	67.69	60.84	148.82	199.00
	4.55−	4.75−	3.03	1.93	4.10	5.35+	4.96	2.50−	5.44	5.50−
NA ♀	66.27	64.80	58.95+	51.38	59.47	65.66	69.04	61.21	141.64	188.45+
	3.26	2.80	2.18	1.80	4.59	6.49	6.47	3.74	4.52	6.17
MA ♂	67.41	67.08	60.75−	52.14	57.21	62.31	66.25−	60.55−	140.45+	184.82
	3.06	2.71	1.61	1.14	5.04	6.65+	6.42	3.88	7.34	6.34
MA ♀	67.10	66.50	60.93	52.22	56.43	62.34	65.17	60.83	134.27	173.82
	4.56	4.00	1.77	0.98	5.28	5.92	5.25−	4.50	7.10	10.51
NC ♂	64.71	65.52	59.56	51.94	59.08	64.15−	66.49	61.45−	146.46	190.73
	3.06	3.12	1.79	0.84	3.12	4.11	4.99	2.21	3.67	4.24
MC ♂	61.00	62.26	58.88	51.59	57.50	61.63	63.68	60.47	131.36	163.27
	4.12	4.39	2.55−	1.47	4.01	3.41	5.14	3.30	5.66	5.62

N = normal; M = mongoloid; A = adult; C = child.
Height and length have been recorded in millimeters and all other measurements have been expressed as a percentage of the cranial height through basion.

the maximum cranial height at right angles, to the Frankfort horizontal plane. Similar measurements were made on matching groups of roentgenograms of normal individuals.

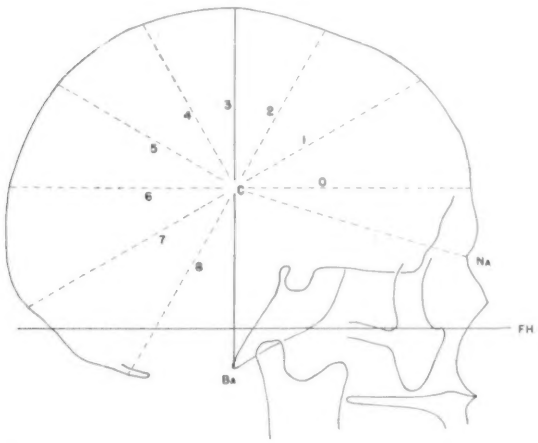

FIG. 1. The method used to measure the lateral cephalometric roentgenograms. Ba = basion; FH = Frankfort horizontal plane; C = mid-point of the cranial height through the basion perpendicular to FH; Na = nasion.

FINDINGS

The measurements have been analyzed by Dr. R. T. Leslie of the Statistics Department of the University of Melbourne and the method employed is described in the Appendix to this paper. The means for the measurements are recorded in Table I. Table II records the "F" values obtained from the discriminant analyses between groups of these radii lying near each other.

TABLE II

"F" FROM DISCRIMINANT ANALYSIS

Groups Compared	Anterior Radii	Posterior Radii	Height and Length
	4,17 d.f.	4,17 d.f.	2,19 d.f.
NA ♂ v MA ♂	0.77	2.05	16.3^{++}
NA ♀ v MA ♀	1.47	1.31	8.62^{++}
NC ♂ v MC ♂	3.04^{+}	0.78	79.4^{++}

d.f. = degrees of freedom; N = normal; M = mongoloid; A = adult; C = child; v = compared with; + = possibly significant difference; ++ = significant difference.

In Table III are recorded the "t" values for those measurements of which the "F" value was significant or nearly so. Superimposed average lateral cranial silhouettes reduced to the same cranial height are illustrated in Figure 2, *A*, *B* and *C*.

There were no significant differences in the relative proportions of the cranium between the groups compared, except that the relative C-nasion distance is just significantly larger (5 per cent level) in the normal than in the mongoloid boys. Mongoloid adult males and females and mongoloid boys, however, have significantly smaller absolute cranial lengths and heights than normal individuals of similar age and the same sex. The "t" values, which are recorded in Table III, are greater for absolute cranial length than absolute cranial height and, while no precise significance can be attached to them, they do reflect the marked differences between the normal and the mongoloid groups in respect to both mean absolute cranial height and length.

While this statistical analysis has indicated that mongoloid boys have a relatively

TABLE III

"t" VALUES FOR THOSE RADII IN WHICH THE "F" VALUE IN THE DISCRIMINANT ANALYSIS FOR THE GROUP IS SIGNIFICANT OR NEARLY SIGNIFICANT

Groups Compared	Height	Length
NA♂ v MA♂	3.04^{++}	5.61^{++}
NA♀ v MA♀	2.9^{++}	3.98^{++}
NC♂ v MC♂	7.37^{+}	12.93^{++}

		Anterior Radii		
	C-Na	0	1	2
NC♂ v MC♂	2.40^{+}	2.00	0.73	0.67

N = normal; M = mongoloid; A = adult; C = child; v = compared with; + = possibly significant difference; ++ = significant difference.

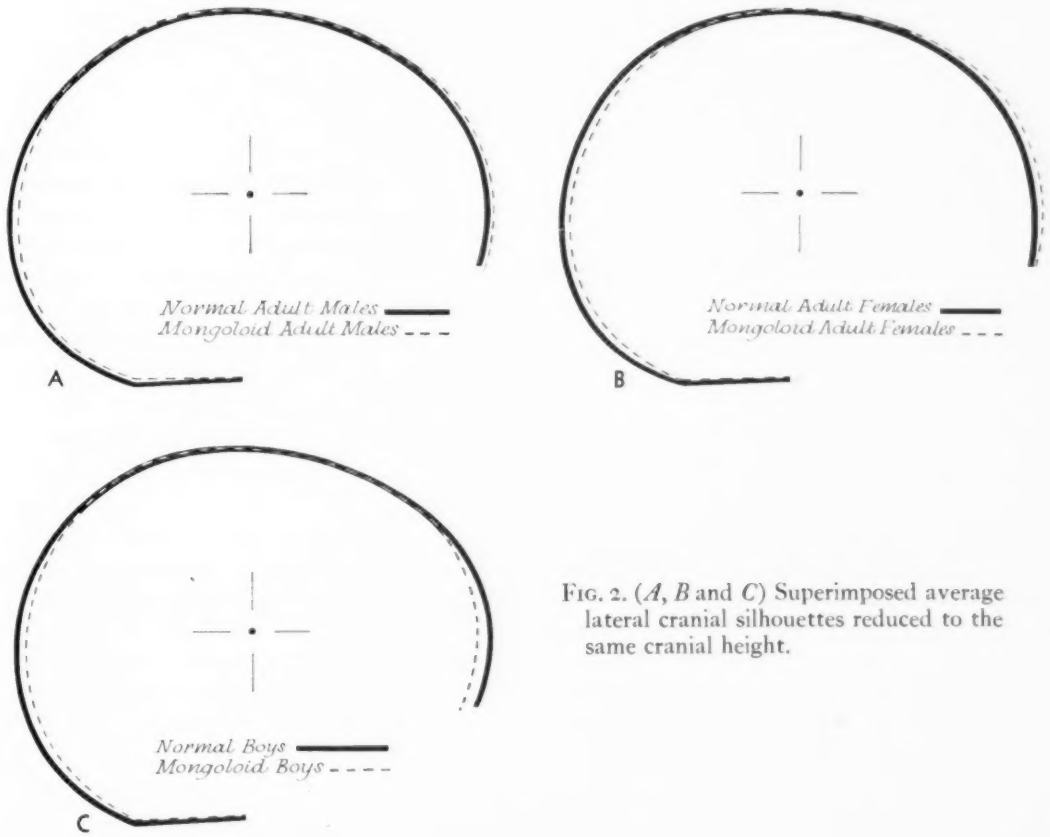

FIG. 2. (*A*, *B* and *C*) Superimposed average lateral cranial silhouettes reduced to the same cranial height.

short C-nasion distance compared with normal boys, it is significant at the 5 per cent level only and since it is occurring as one among 24 possible calculations it may be due to chance.

DISCUSSION

The failure of the statistical analysis to show significant differences between the normal and mongoloid groups may be due to one of three factors—the sample may be too small to demonstrate a small real difference, the variability between individuals may be sufficiently great to obscure a small real difference or no real difference may be present. It must be stressed, however, that a consideration of the size of the sample, together with the individual variation present, makes it clear that any real change visible clinically should have been detected.

Opinions differ among earlier workers as to whether any posterior cranial flattening is present in mongolism. Several who have examined the living have reported such an appearance but no such change has been noted in dried skulls. During this investigation no marked flattening of this region has been detected. The possibility that the soft tissue contour in this area may show some flattening was not studied. Any such flattening cannot be pathognomonic of mongolism since it was found by Bean and Speidel[1] in 9 per cent of normal adult North American males.

SUMMARY

1. The shape of the cranium in white Australian mongoloids has been analyzed by measurements on standardized roentgenograms of 11 boys, 11 adult males and 11 adult females. These were compared with similar measurements on matching groups of roentgenograms of normal individuals.

2. A statistical analysis shows that the forehead may be unusually convex in mongoloid women and the C-nasion distance may be short in mongoloid boys. These differences may, however, be due to chance.

3. In all mongoloid groups the total cranial height and length were significantly below normal values.

4. No departure from normal in the contour of the posterior portion of the cranium was detected.

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Our thanks are due to many who have helped during the course of this investigation, particularly Dr. R. T. Leslie of the Statistics Department of the University of Melbourne and the staff of the Anatomy Department.

APPENDIX

By R. T. LESLIE

The comparison of the cranial silhouettes of two groups comes mathematically to examining differences between two plane closed curves. Several parameters of each curve would have to be estimated to determine the curve best fitting the observed silhouette, and the physical interpretation of such parameters would have to be determined. Moreover, the standard errors of the estimates would be required in order to compare two silhouettes. The alternative method, that of discriminant analysis adopted in this paper, avoids the difficulties of the former approach, and yields results which can be interpreted directly in terms of the anatomic quantities measured. Such questions as "flattening of the posterior region" can be examined by comparison of the radii in the two series of skulls without the intermediary of fitted curves.

There appeared to be no strong objection to considering separately the anterior and posterior regions of the skulls. It should be noted that the conclusions reached will depend on the figures being compared. If direct measurements are used, absolute difference in size will be compared between series. If, however, indices are used which

have already been made relative, shape differences will be compared between series. Thus, employing the measurements of height (H) and length (L) in millimeters, significant differences between series mean that the skulls differ in *size*, whereas when the radii Na, 0, 1, 2 (anterior region) and 5, 6, 7, 8 (posterior region) are compared separately between series, significant differences must be interpreted as *shape* differences.

Discriminant analysis is an extension of simple testing of differences between means, appropriate to the situation where each object of two series of objects is characterized by a multiplicity of measurements. One could compare the values for a particular radius for normal and mongoloid individuals, but a much more efficient utilization of the full information on the two series is possible by making a composite test employing simultaneously the four radii Na, 1, 2, 3. This method has the additional advantage of comparing, between series, what is virtually the curvature of the skull silhouettes. The mathematical procedures are designed to find which of the radii differ most between the series, and then to produce a single index for each series which results from appropriate weighting of the several radii and which maximizes the difference between the two series. The results of the procedure are thus, in the first place, to determine whether a significant difference exists between silhouettes of the two series, and subsequently to yield a rule whereby an unknown silhouette may be classified as belonging to one series or the other, with a computed risk of misclassification.

This is not the appropriate place to discuss details of the calculations of the discriminant functions. Reference may be made to R. A. Fisher, "The use of multiple measurements in taxonomic problems," *Ann. Eugen.*, 1936, *7*, 87–104, or to §39 of K. Mather's book, "Statistical Analysis in Biology," for an elementary discussion. However, it may be noted that the final significance of the discriminant function is evaluated by reference to the F-tables appropriate for tests in the analysis of variance. All experimental results are subject to some type of random variation, which will intrude into measured differences between groups of objects. The (mean) group difference must be evaluated against the known random variability, and is properly quoted as having a certain probability of arising by chance. Thus, if the "F" value of the discriminant function for comparing two skull series is stated to be significant at the 5 per cent level, this must be interpreted to mean that on the average such a difference could arise between two *identical* series by chance 5 per cent of the time. Similarly, a "t" value quoted for the difference between means of a single radius between two skull series has a certain probability attached to it, *e.g.*, if it is stated to be significant at the 1 per cent level, there is a probability of 1/100 that it arose as a result of a chance difference between the two skull series.

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NONMETRICAL OBSERVATIONS ON CRANIAL ROENTGENOGRAMS IN MONGOLISM*

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SINCE the introduction of roentgenography into medical practice and research, a voluminous literature has accumulated concerning the bony structural changes which can be detected in the victims of disease. In mongolism, however, this method of investigation has been employed infrequently and on comparatively small groups of individuals.

REVIEW OF THE LITERATURE

1. *Sutures.* Soon after birth the sutures may be gaping and more open in mongoloid than in normal infants (Benda[7]) and may be late to close and late to unite (Fraser,[18] Muir,[24] Chartier,[13] Brudzinsky,[11] Clift,[14] von Hofe,[20] Brousseau,[10] Warner[34] and Benda[6]). On the other hand, Spitzer and Robinson,[30] from a roentgenographic study of 15 male mongoloids aged 7.75 to 14.5 years, reported normal sutures in all except one boy aged 8 years with "delayed union" and one boy aged 14.5 years with sutures "not fully united." Among 12 female mongoloids of similar ages they reported normal sutures in all except one girl aged 8.5 years in whom the sutures were "open," one girl aged 16.75 years in whom they were "not quite united" and one girl aged 28 years in whom "delayed ossification" was recorded. Their report is limited in value by failure to indicate the sutures to which they are referring.

2. *Metopic Suture.* The metopic suture in mongoloids is usually widely gaping at birth and is usually palpable almost as far as the frontonasal suture (Benda[7]). In addition, it is late to close and late to unite (Warner,[34] Benda[6]).

Bourneville[8] claims that metopism is usually present. Although no reference is made to this feature by more recent investigators, it should be noted that metopism was present in the skull described by Fraser[18] and in 2 of 3 skulls described by Greig.[19]

3. *The Margins of the Cranial Bones.* Irregular rarefied areas have been noted frequently along the margins of the cranial bones in roentgenograms of mongoloids (Brudzinsky,[11] Schuller,[27] Clift,[14] Benda[6]). Such changes were not present in the 3 skulls examined by Greig.[19]

4. *Sutural Bones.* Numerous sutural bones were present in the case reported by Fraser[18] and in 2 of the skulls described by Greig,[19] but such bones are also common in normal individuals. In one of the skulls reported by Greig, four small sutural bones were related to the inferior end of the metopic suture where they are unusual in normal individuals.

5. *Frontal Sinus.* Benda[5,6] noted that the frontal sinuses were more often absent than in normal individuals; their absence in a single case was reported by Thomas.[32] In Spitzer and Robinson's series[30] of 15 male and 12 female mongoloids, aged 7.75 to 14.5 years and 8.5 to 29 years, respectively, a frontal sinus shadow was visualized in only 1 with certainty and doubtfully in another 2.

MATERIAL AND METHODS

The findings reported in this paper form part of those obtained during a long term comprehensive study of the physical growth of mongoloid idiots. These mongoloids are second generation Australians living in Melbourne.

The described features have been observed in lateral head roentgenograms

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taken with the aid of a Bolton-Broadbent cephalometer (Broadbent[9]). Such roentgenograms of 30 male and 41 female mongoloids have been included in the investigation. The age range of these individuals is shown in Table 1.

Table I

NONMETRICAL FEATURES OF CEPHALOMETRIC ROENTGENOGRAMS

Number present/Number observations

Age Range in Years	Metopic Suture Present	Sutural Bones Present	Frontal Sinus Present	Superciliary Arch Present
Males				
2–5	4/4	0/8	0/10	0/10
5–10	1/5	0/8	0/9	0/9
10–15	4/8	2/8	0/10	0/10
15–20	5/7	1/10	1/10	5/10
20+	5/6	1/10	0/11	11/11
Females				
2–5	1/1	0/1	0/1	0/1
5–10	2/2	0/5	0/5	0/6
10–15	10/20	2/26	4/28	3/27
15–20	1/6	2/10	2/11	1/10
20+	5/12	0/15	2/17	1/17

FINDINGS AND DISCUSSION

1. *Sutures.* The sutures were wider than usual at ages when they are open in normal children. The appearances suggest that the growth changes in the sutural areas are normal in type but are spread over a longer period than in normal children.

2. *Metopic Suture.* Among the 21 males and 38 females over the age of 10 years, metopism was seen in 14 of the former and in 16 of the latter (Table 1). Since metopism is present in 8.8 to 12.3 per cent of adult western European crania (Martin[22]), our findings and those of Bourneville[8] demonstrate that metopism is unusually common in mongolism.

Bryce and Young[12] reported a "well marked" post-coronal constriction in 31 of 76 metopic skulls. While such a constriction may occur in normal skulls, they considered that it was more common in metopism. Such an association was not seen during this study.

That the abnormal form of the mongoloid cranium is not due to the frequent occurrence of metopism in these children is supported by evidence that metopism is not linked with major alterations in cranial form in presumably normal individuals (MacDonell,[21] Parsons,[25] Bryce and Young[12]).

3. *Margins of the Cranial Bones.* Irregular rarefied areas were not detected along the margins of the cranial bones. These findings are consistent with most earlier reports.

4. *Sutural Bones.* No sutural bones were detected until after the age of ten years and then only in the lambdoid suture. The findings indicate that these bones occur with approximately the same frequency as in normal individuals (Table 1).

5. *Frontal Sinus.* A frontal sinus shadow was not seen until after the age of ten years and only then in 1 of 31 males and 8 of 56 females (Table 1). In the remainder the sinuses were either congenitally absent or their appearance grossly delayed. In view of the statement by Samuel[26] that the absence of one sinus is "fairly common" and that both are "more rarely" absent, one must conclude that an absence of the frontal sinuses, or a marked delay in their development, is unusually common in mongoloids. In 1 female both frontal sinuses and the sphenoid sinus were unusually large; such a condition is rare in mongolism and is illustrated in Figure 1, *A* and *B*.

Weinmann and Sicher[35] consider that the development of the superciliary arch is related to the transmission of masticatory forces but the split-line preparations of Tappen[31] show that the arrangement of the haversian systems in this area is not consistent with such an interpretation. It has been claimed (Weinmann and Sicher,[35] Samuel[26]) that, if the arch is absent or small, the frontal sinus will also be absent or small. Our findings are in agreement with this opinion since the superciliary arch was poorly developed except in the presence of a frontal sinus shadow.

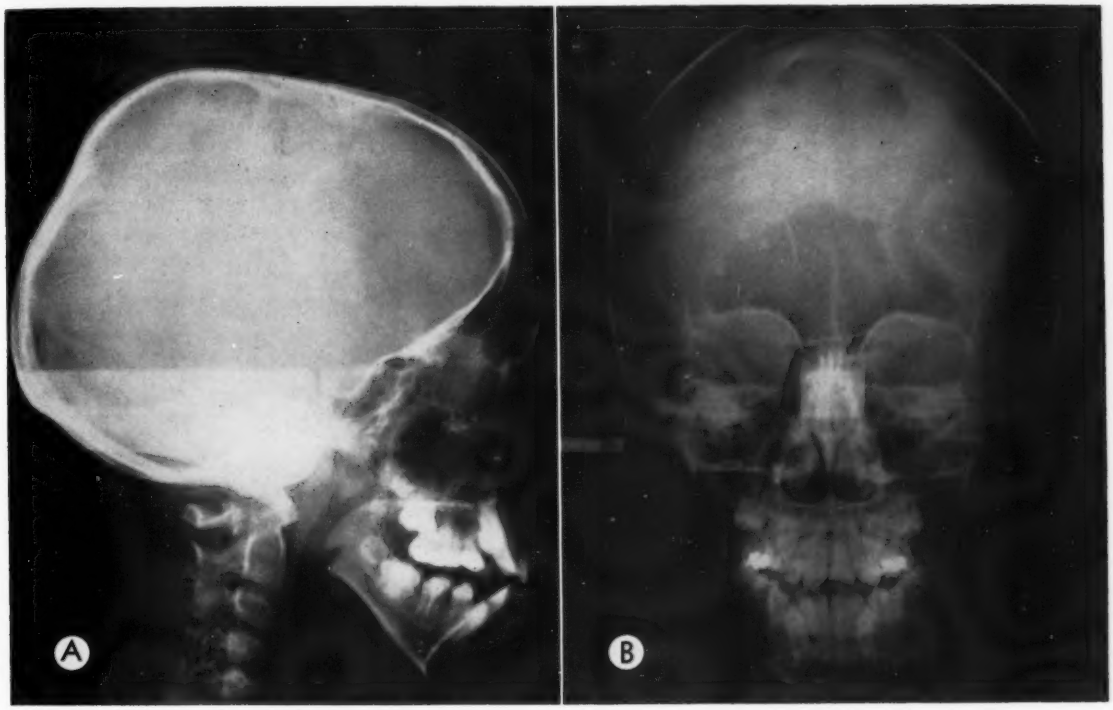

Fig. 1. (*A* and *B*) Cephalometric roentgenograms of a mongoloid girl showing large frontal and sphenoidal sinuses.

Le Double[16] and Samuel[26] consider that bilateral absence of the frontal sinus is usually associated with a persistence of the metopic suture. Schuller[28] concluded from a study of roentgenograms of normal adults that "in the presence of a metopic suture the frontal sinuses, if they are developed, will be small, never passing over the midline from one side to the other side." Both changes are common in mongoloids, but the frontal sinus is also often absent when the metopic suture is obliterated.

In children suffering from hyperpituitarism (Weinmann and Sicher[35]), the changes in the superciliary arches and frontal sinuses appear to be the reverse of those observed in mongolism. Further evidence of an experimental nature (Mortimer,[23] Becks *et al.*,[4] Collins *et al.*,[15] Evans *et al.*,[17] Asling *et al.*,[1] Walker *et al.*,[33] Simpson *et al.*,[29] Asling *et al.*[2] and Asling and Evans[3]) suggest that a pituitary deficiency may be operating in mongolism. This forms the theoretic basis for the administration of pituitary extracts recommended by Benda.[7]

SUMMARY

1. Lateral roentgenograms of the crania of white Australian mongoloids have been used to assess the nonmetrical features associated with this condition.

2. During early life the sutures were more widely separated than in normal children, rarefied areas were not noted, nor were sutural bones more common than usual.

3. After the age of ten years, a metopic suture was present in 42 per cent of the females and in 67 per cent of the males while the frontal sinuses were absent and the superciliary arches poorly developed in 30 of 31 males and 48 of 56 females.

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HISTIOCYTOSIS X*

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THE history of the discovery of histiocytosis X as a disease entity and the changing concepts regarding its etiology and pathogenesis are almost as interesting as the varied manifestations of the disease itself.

Lichtenstein,[41] in a review of the literature up to 1953, suggested the name histiocytosis X for the group of diseases known as Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma, based on his own and the correlated pathologic findings of others.

HISTORIC REVIEW

Hand,[31] in a paper titled "Polyuria and Tuberculosis," described a phase of this disease entity for the first time in 1893. The case was that of a boy aged three years with a recent history of diabetes insipidus, exophthalmos, bronzed dry skin, hepatosplenomegaly, distended abdomen, and poor development. It was his impression, based on subsequent postmortem cranial and pulmonary findings, that this was an atypical form of tuberculosis. Hand,[32] in 1921, reviewing his old case and one of Kays in 1905 which presented very similar findings, agreed with Schüller[53] (1915) and Christian[9,10] that this was a previously unrecognized disease entity. He disagreed with Schüller's contention that this was a disease of primary pituitary dysfunction and his arguments specifically noted the absence of diabetes insipidus in some cases and the presence of osseous lesions before the onset of diabetes insipidus in others. His theory suggested that the diabetes insipidus was due to secondary pituitary involvement by the disease process. Thompson, Keegan and Dunn[59] were in agreement with Hand's theory that this was not a disease of primary pituitary origin. In their case of a nine year old boy with diabetes insipidus, exophthalmos, and defects in the cranial bones—the classic triad identified with Hand-Schüller-Christian disease, there was no evidence of involvement of the pituitary gland by the infiltrative process. They noted that there was involvement of the hypothalamus and suggested that the diabetes insipidus had its origin secondary to hypothalamic involvement. Schüller,[52] reviewing his own cases, that of Christian and one of Hochstetter in a thirty-eight year old male, maintained that the disease was of primary pituitary origin and he called it "dysostosis hypophysaria." In 1928 Rowland[51] referred to this disease as a xanthomatous degeneration of the skeleton and suggested that ingested lipids might be causally related to its origin. He noted that lipidization of the histiocyte was an important manifestation of the disease.

Cowie and Magee,[12] in 1934, in analyzing the postmortem material of Lichty[42] for lipid content, found that the uninvolved tissues had normal total lipids, cholesterol, and phospholipids, and that the involved areas had a very high lipid content, 50 per cent of which was cholesterol. This fact was substantiated subsequently by Freud *et al.*[23] in 1941. In 1935 Smith[56] classified Hand-Schüller-Christian disease as a lipoid histiocytosis. Thannhauser and Magendantz,[58] in 1938, categorized the disease as a primary essential xanthomatosis of the normocholesteremic type. In their opinion, the hypothesis that primary essential xanthomatosis was a disorder of cholesterol metabolism had not been proved. They felt that a primary hereditofamilial disorder of the intracellular enzyme system concerned with the formation of cholesterol within the

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histiocyte or reticulum cell predisposes to the abnormal accumulation of cholesterol and thus transforms it into a xanthoma cell.

Attention up until this time had not been directed to the possibility that the Hand-Schüller-Christian disease might be related to Letterer-Siwe disease, despite the fact that Letterer[39] described his first case in 1924 and Siwe[55] reported a group of cases in 1933. In fact, it was Abt and Denenholz,[1] in 1936, who reviewed the literature and placed under a single nosologic entity that disease of children which is manifested by hepatosplenomegaly, petechiae, anemia, multiple osseous lesions and lymphadenopathy and which they called Letterer-Siwe disease. In 1940 Wallgren[62] and Hansen independently came to the conclusion that Hand-Schüller-Christian disease and Letterer-Siwe disease were related manifestations of similar disease processes.

In the same year Lichtenstein and Jaffe[40] suggested the name eosinophilic granuloma to describe a new bone lesion which they had personally observed. In a review of the literature at that time they recorded cases of Finsy in 1929, Mignon in 1930, Schoirer in 1938 and Otani and Ehrlich which fit the pathologic criteria for the new disease which they were describing. Shortly thereafter Farber,[20] Gross and Jacox[29] and Mallory[43] further corroborated the previous impressions of Wallgren that Letterer-Siwe disease, Hand-Schüller-Christian disease and now eosinophilic granuloma were probably manifestations of the same basic disease process. Lichtenstein[41] in 1953 correlated the investigations of all the previous observers based on their histopathologic material and concurred with the most recent opinions that these disease processes had their origin in a type of inflammatory histiocytosis and are actually different phases of the same basic disease process. He proposed the term "histiocytosis X" to include all of these disease entities.

CLASSIFICATION

It is evident from the previous discussion that until 1940 eosinophilic granuloma was not recognized as such and that Letterer-Siwe disease had not been seriously considered to be related to Hand-Schüller-Christian disease. It was for this reason that no classification to include either of these diseases had been considered up until that time.

Hand-Schüller-Christian disease had been called by a multitude of names, most of which described the clinicopathophysiology of the disease or conjectured regarding its etiology. These included; dysostosis hypophysaria, xanthomatosis, lipoid histiocytosis, lipoidosis, lipoid granulomatosis, primary granuloma, xanthomatosis, reticuloendotheliosis and others.

In 1930 Sosman[57] classified the xanthomatoses to include: Gaucher's disease, Niemann-Pick disease, Schüller-Christian disease, xanthoma of diabetes, pregnancy and jaundice, and essential xanthomatosis. Sosman further stated that important to the classification of xanthomatoses were hypercholesteremia and normal cholesterol associated with traumatized or suppurative areas capable of storing it as a foreign body.

Mallory,[43] in 1942, classified this group of diseases according to age incidence and the nature and distribution of the lesions: (1) Letterer-Siwe disease occurs in infancy and is characterized by diffuse soft tissue involvement and rapid fatal termination; (2) Hand-Schüller-Christian disease is a chronic form of the disease process found in both membranous bone and soft tissues and is primarily seen in children and young adults; and (3) eosinophilic granuloma is a disease found in bone, with little or no involvement of the soft tissues, and occurs in children and young adults.

In 1944, Engelbreth-Holm *et al.*[19] agreed with the previous impressions that the pathology of Hand-Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma was interrelated and suggested a classification of all these based on the histologic findings in the evolution of the disease: (1) the hyperplastic proliferative stage in which reticulohistiocytosis is prominent and in which eosinophilic infiltration might occur; (2) the granuloma

stage; (3) the xanthomatous stage where lipid deposition occurs; and (4) the fibrous stage of healing.

Lichtenstein,[41] in 1953, classified the histiocytoses into three phases of a single basic disease process: (1) histiocytosis X localized to bone (eosinophilic granuloma); (2) disseminated chronic histiocytosis X (Hand-Schüller-Christian disease); and (3) disseminated acute and subacute histiocytosis X (Letterer-Siwe disease).

The latter classification tends to restrict eosinophilic granuloma to a type of localized disease of bone. Since this classification, however, cases of eosinophilic granuloma with multiple osseous lesions and asssociated with visceral involvement have been reported.[4,7,26,33,44,49] Cases of eosinophilic granuloma without osseous pathology and simple visceral involvement have also been reported.[38,44,45]

A more current classification, based on that of Lichtenstein, could include the phases of this disease as they manifest themselves with regard to the age incidence and prognosis: (1) Letterer-Siwe disease, an acute disseminated disease of infants involving both osseous and soft tissue with the soft tissue lesions predominating and having a poor prognosis; (2) Hand-Schüller-Christian disease, a disseminated disease of children and young adults having a more chronic course and a generally better prognosis than that of Letterer-Siwe disease; and (3) eosinophilic granuloma, a chronic disease of children and young adults with the lesions most often osseous and monostotic. In this group the prognosis is excellent; when the lesions are multiple or visceral the prognosis is similar to that of Hand-Schüller-Christian disease.

PATHOLOGY

The closely related histologic findings of Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma make it difficult to describe with certainty under any of the disease entities that one histologic picture which is typical of that particular disease.

In the early phase, characterizing the acute form known as Letterer-Siwe disease, the histologic picture is that of a generalized proliferation of large lipoid and nonlipoid storing reticulum cells. The microscopic field usually contains a moderate number of multinucleated giant cells, leukocytes, reticular fibers and areas of necrosis. The presence of foam cells, collagenization and scarification indicates that the lesions are older and are more closely related to the Hand-Schüller-Christian, or chronic phase, of the disease. In the latter, the lipidized histiocytes seem to collect around small blood vessels. The rapid proliferation of these cells is seen to replace normal tissue and may be so severe as to decompensate the normal bone marrow and produce hematologic manifestations.

The presence of an abnormal accumulation of eosinophils and histiocytes associated with focal areas of necrosis with or without histiocytic lipidization categorizes this histiologic picture with the group known as eosinophilic granuloma. It should be pointed out that the presence of eosinophils is not unusual in Hand-Schüller-Christian disease and, although sparse in the reticulum cell laden Letterer-Siwe disease, they are found here also. Similarly, the presence of lipidized cells is not confined to Hand-Schüller-Christian disease. With special stains the early accumulation of fat can be demonstrated in the reticulum cells both in Letterer-Siwe disease and eosinophilic granuloma.

In several cases reported without therapy, biopsies from many areas in the same patient demonstrate "pure" histologic characteristics of Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma.

In reviewing the histologic material in our own cases of Hand-Schüller-Christian disease, the tissue specimens obtained were most characteristic of the chronic phase of the disease with the presence of collagenized, scarified and lipidized tissue predominating.

CLINICAL FINDINGS

The findings in our group of cases of

Hand-Schüller-Christian disease have been atypical if one considers the classic triad to be typical of the disease process. From a review of the literature, however, it is evident that less than 10 per cent of the cases have presented the triad of findings of diabetes insipidus, exophthalmos, or cranial defects concurrently. Most often, the presenting complaint is related to one or two manifestations of the triad, but not to all three.

Case 1 presented as a case of migratory polyarthritis with clinical findings consistent with those one would expect in a rheumatoid arthritic process. On numerous occasions the patient was noted to have hot, tender, swollen, red joints. On occasion the distribution was bilateral and symmetrical. The only external manifestation was the presence of numerous yellowish white skin nodules which appeared over the scalp, face and trunk as the disease progressed. The patient did extremely well following initial roentgen therapy to the skull, which had multiple calvarial defects demonstrated roentgenographically. He has been very active, attending school daily, and has had no recurrent bouts of migratory polyarthritis since his first course of irradiation. The family denies that the child has been incapacitated in any way by the disease.

Case 11 presented with no specific findings which could be related to histiocytosis. She was first seen by her own physician who felt that the child had acute poliomyelitis because of signs of meningismus, weakness of the abdominal muscles and facial weakness. After what was considered a suitable clinical interval, the patient was admitted and discharged from the hospital where the clinical impression was consistent with acute poliomyelitis and where she received physiotherapy. The patient was readmitted to the hospital two months later with the findings much worse than they had been previously. Roentgenograms at this time revealed destructive lesions of the skull and cervical spine. A neurosurgical evaluation was consistent with that of a diffuse metastatic disease process involving both the brain and spinal cord. It was only after complete roentgenographic examination of the entire skeleton that the diagnosis of Hand-Schüller-Christian disease was suggested and later corroborated by biopsy study. Despite a course of roentgen therapy limited to 200 r to 400 r to most of the involved areas, the patient expired three years later with autopsy findings related to aplastic anemia secondary to bone marrow replacement by the disease process.

Most of the cases which we have had the opportunity to review have also had varied initial complaints but, in almost all instances, diabetes insipidus, skin lesions, enlarged liver and spleen, bone pain, exophthalmos, loose teeth, persistent draining ear, weakness, weight loss, anorexia, disturbance of growth, and other signs of a chronic debilitating disease were present as a total clinical picture or in some combination to suggest histiocytosis as a differential diagnostic consideration.

We know that the clinical manifestations of any phase of this disease are related directly to the organ system involved. Bone pain, the most common complaint, has its origin secondary to replacement of normal bone by the hyperplastic reticuloendothelial cells. Exophthalmos is apparently related to the retro-orbital invasion of proliferating lipidized histiocytes. Loose teeth similarly are related to involvement of the maxilla or mandible by the replacement phenomena to produce the roentgenographic finding of "floating teeth." Diabetes insipidus and disturbances of growth can be traced to involvement of the hypothalamus or pituitary gland by the disease process. Chronic draining ear, a very common complaint, is apparently related to destruction of the petrous portion of the temporal bone and involvement of the middle ear. Certainly, the lymphadenopathy, hepatomegaly, splenomegaly and diminished pulmonary function are related to direct involvement of these organs by the reticulosis.

We can see a very definite similarity in the clinical picture of the disseminated forms of Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma. The similarity of findings further tends to amalgamate present opinions that these separate nosologic disease entities are really manifestations of the same basic disease process.

In the cases of eosinophilic granuloma presented as a monostotic osseous form of the disease, the patients all had the same complaint, *i.e.*, pain and limitation of extremity motion. This complaint appears to be by far the most common in this phase of the disease.

ROENTGENOGRAPHIC FINDINGS

We believe that the evolution of the phases of the histiocytoses can be related to specific roentgenographic findings. The earliest lesions that one sees in all three forms of the disease are those of medullary areas of rarefaction of both the membranous and long bones. These appear as small "lakes" which, in some lesions, are sharply marginated and scalloped and, in others, are ill defined on the periphery, tending to shade with normal bone (Fig. 1). As the lesions get larger and older they may produce the appearance of cystic expansion of the long bones and flat bones. In other lesions, simple scalloping of the inner cortex is evident with extension of the areas of replacement proximally and distally in the diaphysis and metaphysis and with no significant alteration in the size or shape of the bone involved (Fig. 1 and 3). In some of the cases which have been reported, areas of reactive sclerosis appear in conjunction with areas of lysis and, when associated with periosteal proliferative bone change, they may simulate Ewing's tumor or osteomyelitis. Our case of eosinophilic granuloma of the tibia is an example of this type (Fig. 11). In the oldest lesions or those that have had specific therapy, a type of pagetoid change is occasionally seen. In almost all cases, if there is a bone healing phase, it simply occurs without residual osseous deformity and with a return of normal bony architecture.

Fig. 1. Case 1. Lesions of Hand-Schüller-Christian disease, seen in various stages of development, include the early, small, ill-defined "lake," the later better defined lesion with slightly sclerotic margins, and the older lesion with moderate reactive sclerosis and coarsened trabecular pattern.

In the skull, the early lesions are usually punched out and, unlike the lesions in the long bones, are not confined to the diploë. The lesions here perforate the inner and outer tables of the skull early and the soft tissue tumefaction felt in the cranial areas usually corresponds to defects in the cranial bones seen on roentgenograms. As the cranial lesions get older they produce large defects which are serpiginous in outline and are often referred to as the "geographic" skull (Fig. 4, 6 and 7).

In 2 of our cases, involvement of the sella turcica was evident. At no time in these cases were there signs of diabetes insipidus or growth disturbance. In one there was moderately extensive involvement of the facial bones and maxilla, but

FIG. 2. Case 1. One year after deep roentgen therapy to the skull, the lesions in the long bones show regression.

there were no signs of loose teeth. In the same patient there was involvement of the petrous portion of the temporal bone; the patient did have a chronic draining ear.

In previous publications it has been said that lesions below the knee are rare, that cervical vertebral destructive changes are also unusual and that the epiphyses are very rarely involved in Hand-Schüller-Christian disease. In our 2 cases of Hand-Schüller-Christian disease there was involvement of the epiphyses at some phase in the disease process. (Fig. 1, 3 and 9). In 1 there was extensive involvement of the cervical vertebrae. (Fig. 7). In 2 cases, lesions were demonstrated both below the knee and in the short bones of the hands and feet (Fig. 1 and 5).

We have followed a case of vertebra plana for years in which we feel that the basic disease process is that of eosinophilic granuloma.[5,11,16] In this case, the replacement phase (Fig. 13), the collapse and "vanishing" phase (Fig. 14) and the regenerative phase (Fig. 15) are all demonstrated. We have no biopsy in this case; however, healing of the lesion occurred without specific therapy except for bed rest and is consistent with the description of Compere *et al.*[11] for eosinophilic granuloma of vertebrae.

The pulmonary manifestations of all phases of the histiocytoses are interesting for the reason that they were described by Hand in his first paper and were not referred to again for many years. The lesion most often appears as an ill-defined infiltrative process which may or may not respond to roentgen-ray or steroid therapy. As the lesion gets older, a honeycombing effect[63] is produced which is now considered to be more typical of the histiocytic process in the lung, although not specific for this disease entity.

The roentgen findings then, except in some cases of eosinophilic granuloma, are usually disseminated and have features

FIG. 3. Case 1. Lesions in the upper humeral shaft with serpiginous outline, producing scalloping of the inner cortex.

specific enough at least to include the histiocytic disease phases in the differential diagnosis when the clinical manifestations suggest a combined type of osseous and visceral disease in children and young adults. In the medullary type of monostotic diaphyseal bone lesion, eosinophilic granuloma should always be a differential consideration.

TREATMENT AND PROGNOSIS

The treatment of histiocytosis has remained relatively unchanged since the first reports of roentgen therapy by Sosman[57] in 1930. He indicated that roentgen therapy arrests the progress of the disease in some patients and will produce permanent or temporary remission in other patients. Childs and Kennedy[8] in 1951 indicated that roentgen therapy should be tried in all cases of histiocytosis and that, if these lesions will respond, they will respond to relatively small doses. They emphasize that the lower the dose of roentgen rays which can be used effectively, the less likelihood there is of damage to the growing bones.

More recently, treatment with corticosteroids was found to be effective, particularly in Letterer-Siwe disease, and to date, out of a total of 17 patients reported treated with the steroids, 7 are known to be alive and very definitely improved.[2,3,37,46] The additional 10 patients who also received steroid therapy did show initial subjective improvement but subsequently demonstrated no clinical response and the drug was withdrawn.

Mermann and Dargeon,[46] in discussing the management of certain nonlipoid reticuloses, stated that in their series of patients, nitrogen mustard produced considerable objective improvement in a patient with Letterer-Siwe disease.

We have, in our small group of patients, tried to follow the roentgen therapy principles set forth by Childs and Kennedy in the treatment of this disease. Our three and one-half year old female patient (Case 11), who received roentgen therapy in two separate courses to multiple areas, showed

Fig. 4. Case 1. Multiple calvarial defects including involvement of the facial bones, sphenoid and the petrous portion of the temporal bones.

immediate subjective improvement and in some areas roentgenologic improvement following the first course of treatment. The total maximum dose to any one area was 400 r in air. The second course of roentgen therapy relieved pain temporarily, but the patient showed rapid deterioration with the development of aplastic anemia, sepsis and death. In this particular case, it was evident clinically and roentgenographically that the aplastic anemia was related directly to the extensive marrow replacement in almost every osseous structure by the disease process.

Our six year old male patient (Case 1) has never been debilitated in any way by the disease since his first course of deep roentgen therapy. He has shown no significant progression of the disease in the interval and, in fact, during the course of deep roentgen therapy to the cranium there was regression of the disease in the long bones.

In the monostotic form of histiocytosis, as is seen in eosinophilic granuloma, excision is usually completely effective (Fig. 17 and 18). It is our opinion that this should be the treatment of choice. If, following surgery, there is evidence of recurrence or incomplete excision, deep roentgen therapy

Fig. 5. Case 1. Unusual involvement of the epiphyses, metacarpals and phalanges.

should be employed in a protracted fractionated manner not to exceed a total depth dose of 1,200 r to the lesion.

We have not had the opportunity to treat a case of histiocytosis with either the corticosteroids or radiomimetic drugs such as nitrogen mustard. It would appear, however, that in those cases where there is generalized disease present, either in the acute or chronic phase, treatment should commence with the corticosteroids based on the excellent clinical summaries described elsewhere. If this is found to be ineffective, it might be well to use radiomimetic drugs such as nitrogen mustard or to use either intravenous or oral doses of radioactive phosphorus (P^{32}) in a manner similar to that used in the treatment of leukemia in children. Certainly, if therapy with P^{32} is considered, a preliminary tracer study should be performed with P^{32} to determine the degree of differential uptake in the abnormal tissue as compared to normal tissue. It seems more rational to us to treat a disseminated disease process with a form of radiation which is multifocal rather than to use multiple port roentgen therapy with repeated doses over a prolonged period.

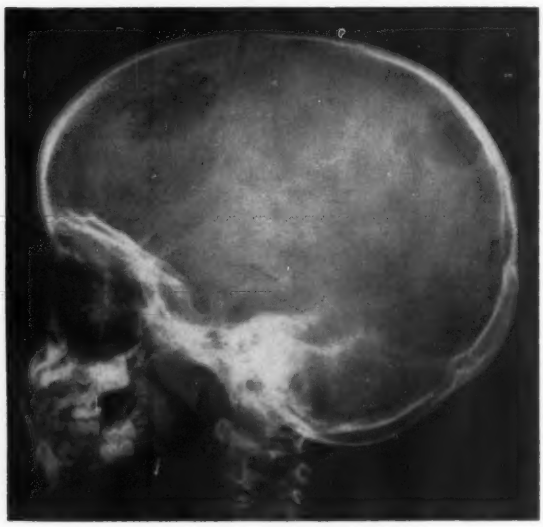

Fig. 6. Case 11. "Geographic" lesions in the frontal and parietal bones.

Finally, if therapy with either the corti-

costeroids, P^{32} or radiomimetic drugs is unsuccessful, external irradiation in the form of deep roentgen therapy should be utilized in small, fractionated, protracted doses similar to those described by Childs and Kennedy.

REPORT OF CASES

Case 1. J.M., a six year old male, was first seen at St. Charles Hospital in Brooklyn, New York on November 18, 1957 with the chief complaint of migratory polyarthritis.

The mother stated that the child was well until one year prior to admission when he developed pain in the knees which was associated with redness and tenderness. There was a moderate elevation of temperature during these episodes to 103°F. which subsided with "powders" and "capsules." The patient subsequently developed similar signs in the small joints of the hands and elbows which lasted from three to four weeks and were relieved in a similar manner.

Four months prior to admission, following roentgenologic study, the patient was hospitalized elsewhere where biopsy of the distal right femur was performed. The pathologic diagnosis was "consistent with that seen in polyostotic fibrous dysplasia of bone." Roentgenographic studies which included the skull, made immediately after the biopsy, were thought to be "consistent with multiple myeloma, reticulum cell sarcoma, or hyperparathyroidism."

Fig. 7. Case 11. Marked progression is noted despite deep roentgen therapy after an interval of one and one-half years. Note destructive changes in the cervical spine.

Fig. 8. Case 11. A lesion of the right ilium is seen, but there is no significant involvement of the dorsolumbar spine or hips.

Two months prior to the time we saw him, the patient had had repeated episodes of joint pain and was rehospitalized. At this time yellowish white skin nodules which were demonstrated in the axilla were biopsied. The pathologic report was that of "fibroxanthoma" of the skin. One month later, he again developed joint pains in the knees and hands. The family, after receiving advice to take the child to a warmer climate, decided to seek other medical opinion and brought him to St. Charles Hospital.

Upon admission on November 18, 1957, the patient was referred for roentgenographic study and a diagnosis of Hand-Schüller-Christian disease was suggested, based on the roentgen

Fig. 9. Case II. Nearly two years after Figure 8, there is marked progression of the disease with extensive involvement of the ribs, spine, humeri, pelvis and hips. Note epiphyseal involvement.

findings in the lower and upper extremities (Fig. 1 and 3). On December 3, 1957 skull roentgenograms demonstrated multiple osteolytic lesions involving the cranial bones (Fig. 4) and at this time it was advised that the patient have additional biopsy study. The patient's parents denied any history of exophthalmos, diabetes insipidus, weight loss, or anorexia but did state that he had frequent upper respiratory infections.

Physical examination revealed a well-developed, well-nourished boy in no acute distress. The positive findings were confined to mutiple skin nodules distributed over the scalp, face, abdomen and axilla which varied in size from pinhead to pea size and were firm, yellowish white and freely movable. A systolic murmur which was thought to be functional was heard at the cardiac apex. The extremities failed to reveal any significant pathology except for scars from the previous biopsy study.

On December 12, 1957 a biopsy of the skull was performed. The surgeon reported that, upon exposure of the outer table of the skull, an area of whitish discoloration was noted which, when uncovered, revealed the presence of yellow, soft, pliable multiloculated material which was well demarcated from the normal surrounding bone and which did not perforate the inner table of the skull.

The pathologist's report on the material obtained was "fragments of bone partially replaced by dense fibrous tissue which is occupied in one area by small groups of compact cells having an abundance of foamy cytoplasm. There are multinucleated giant cells seen frequently with eosinophils." The diagnosis was Hand-Schüller-Christian disease.

The patient was then referred to the general staff conference for opinion regarding therapy and it was suggested that deep roentgen-ray therapy be given to the areas which were painful.

Roentgen therapy was administered utilizing the following factors: 200 kv. peak, 20 ma., with 0.5 mm. Cu and 1.0 mm. Al filtration, half value layer 0.9 mm. Cu. A target skin distance of 50 cm. was used to direct the beam to the right and left sides of the skull through a 10×15 cm. port. The patient received a total air dose

Fig. 10. Case II. Multiple femoral shaft involvement with a lesion in the upper femoral shaft resembling osteomyelitis or Ewing's tumor. The latter is similar to a lesion of eosinophilic granuloma (Fig. 11).

of 1,200 r to the lesions of the right and left hemicranium.

Following the initial course of therapy the patient did well (Fig. 2) and was asymptomatic to June, 1958 when he developed diminished hearing in his left ear. An ear, nose and throat consultant suggested a tonsillectomy. In February, 1959, after frequent upper respiratory infections, the patient had a tonsillectomy and improved significantly.

Laboratory findings on December 11, 1959 were: red blood cell count 3,560,000, hemoglobin 11.45 gm., white blood cell count 8,400, urine negative, Wasserman negative, sicle cell preparation negative. On December 17, 1957 calcium was 9.3 mg. per cent, phosphorus 4.6 mg. per cent, alkaline phosphatase 3.5 KA units, total protein 7.8 gm., albumin 4.6 gm., globulin 3.2 gm.

Follow-up roentgenographic studies showed resolution in the number of lytic lesions within the skull and the lesions in the femoral shafts had also undergone regression. The patient remained completely asymptomatic except for the presence of multiple skin nodules which continued to increase during the ensuing period. He is now being followed in the outpatient department of St. Charles Hospital.

Case II. G.M.S., a three and one-half year old female, was first admitted to St. Charles Hospital on December 14, 1952 following an illness which in October, 1952 was diagnosed by the patient's private physician as poliomyelitis. At the time of her admission a residual mild left facial weakness, eye asymmetry, weak abdominal muscles and a "weak right hip" were noted. After one month of rehabilitation therapy the patient was discharged to the clinic.

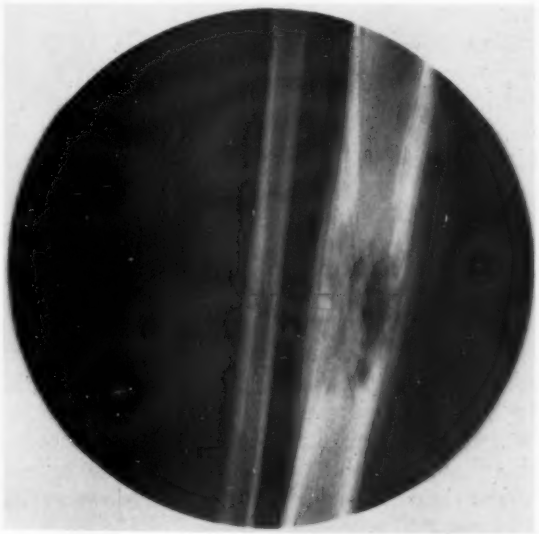

Fig. 11. Case III. Eosinophilic granuloma in which the destructive medullary changes and periosteal proliferative bone change simulate Ewing's tumor.

Fig. 12. Case III. One year following deep roentgen therapy, there is no residual defect.

On February 3, 1953 the patient was seen in the outpatient department and treated for an upper respiratory infection. The mother denied any other complaints at this time. The patient was returned to the clinic on February 9, 1953, with an increasing weakness of the right leg, increasing irritability, and meningismus. Physical examination revealed a difference in the deep tendon reflexes. It was felt that she had a recurrence, probably complicated by the upper respiratory infection, and that readmission and possibly more rehabilitation were necessary.

Roentgenograms of the pelvis and entire spine made on February 9, 1953, revealed a lesion of the right ilium which was thought to be consistent with a metastatic process, although the possibility of Hand-Schüller-Christian disease was not ruled out (Fig. 8). Neurosurgical consultation suggested meningoencephalomalacia secondary to metastatic disease.

Roentgenograms of the skull made on April 2, 1953, showed "geographic lesions" in the frontal and parietal bones (Fig. 6).

Open biopsy was performed on December 16, 1953 and a histologic picture consistent with eosinophilic granuloma or Hand-Schüller-Christian disease was described. Roentgen therapy was advised.

The patient showed temporary subjective improvement following deep roentgen therapy to the skull (400 r in air), thorax (400 r in air), pelvis (400 r in air) and cervical spine (400 r in air).

One year later she was readmitted to the hospital with tenderness over the dorsal spine, extremities and left clavicle. Repeat roentgenographic examination at this time confirmed the clinical impression that there had been marked progression of the lesions (Fig. 7, 9 and 10).

Additional roentgen therapy was administered over the spine and pelvis. The total dose did not exceed 400 r in air in any of these areas. Again there was temporary improvement, lasting about two months. At that time the patient was placed in a body spica for relief of pain, particularly of the dorsal spine. Repeated measurements of urinary output failed to reveal any evidence of diabetes insipidus.

In February, 1955 the patient developed chicken pox and from this point on the course was that of rapid deterioration with development of profound anemia and leukopenia. In April the platelet count, despite repeated transfusions, was 66,000, hemoglobin 5.8 gm., and white blood cell count 2,700. In June the patient contracted mumps following which the liver and spleen became enlarged. There were repeated bouts of hematemesis and body ecchymoses. In September the platelet count was 13,000, hemoglobin 54 per cent and the patient developed bronchopneumonia. In October a hematoma on the calf was found to be septic upon incision and drainage. In November an absess of the mandible and severe nose bleeds occurred. In December, 1955 the patient expired and an autopsy revealed histopathology consistent with advanced Hand-Schüller-Christian disease involving all organs, with almost complete replacement of the hematologic system by the disease process.

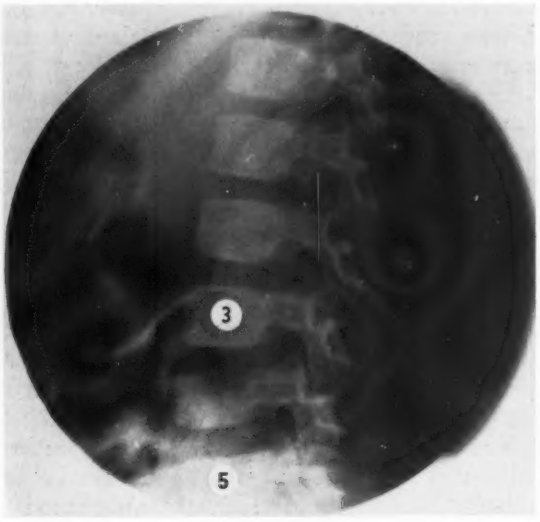

Fig. 13. Case iv. Eosinophilic granuloma of the fourth lumbar vertebra in which there is early spotty destructive change in the centrum. (Reproduced with permission from the *New York State Journal of Medicine.*)

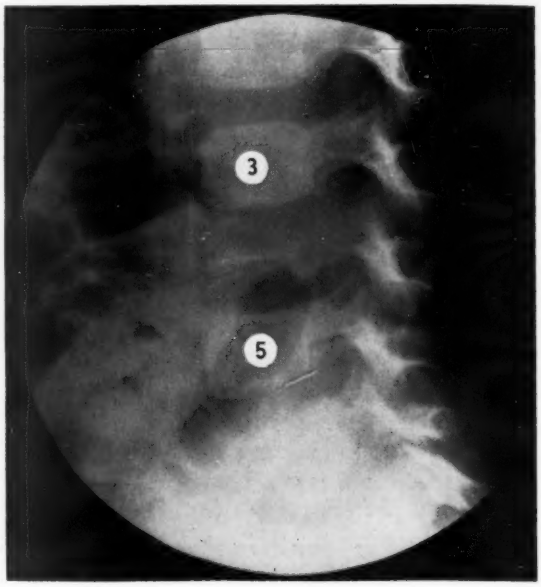

Fig. 14. Case iv. One month after Figure 13, the "vanishing phase" is demonstrated. No therapy except bed rest. (Reproduced with permission from the *New York State Journal of Medicine.*)

Case iii. L.V., a three year old child, was admitted to St. Charles Hospital on August 8, 1954 because of pain in the right lower extremity. Approximately two weeks prior to admission the mother had noted a mass in the region of the right calf which, on examination by the mother, was tender. On admission the positive physical findings consisted of an ill-defined soft tissue fullness over the posterior upper one-third of the right tibia. There was no redness or

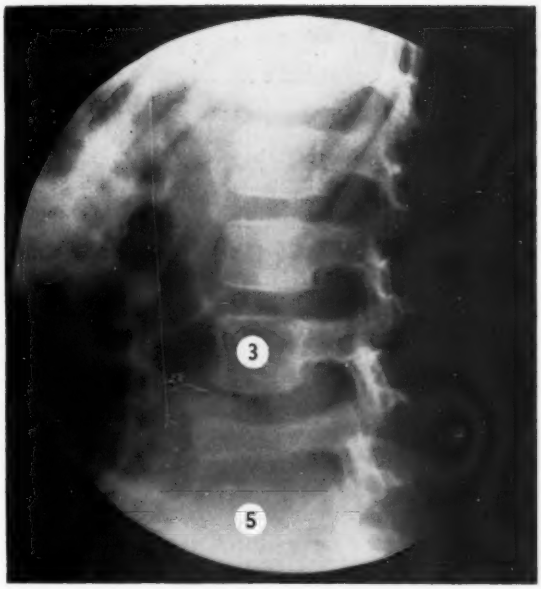

Fig. 15. Case iv. Two years and three months after Figure 14, the regenerative phase is seen with a residual vertebra plana. The patient is now asymptomatic. (Reproduced with permission from the *New York State Journal of Medicine*.)

heat in this region but there was marked tenderness immediately over the central portion of the fullness described. The clinical impression at this time was that of acute osteomyelitis. The white blood cell count was 11,000, hemoglobin 13 gm., tuberculin OT 1:10,000 negative. Roentgenograms of the tibia revealed a medullary destructive lesion in the region of the midshaft of the right tibia associated with endosteal and periosteal proliferative bone change. The roentgenographic impression was that of acute osteomyelitis with Ewing's sarcoma a secondary consideration (Fig. 11).

On August 25, 1954 a biopsy of the right tibia was performed. The surgeon reported cortical expansion at the level of the lesion which was entered with a trephine. Yellowish gray gelatinous material was encountered and removed for microscopic study. The pathologist reported eosinophilic granuloma.

A course of deep roentgen therapy was administered to the lesion from August 27, 1954 to September 13, 1954 utilizing the following factors: 200 kv. peak, 20 ma., 0.5 mm. Cu and 1 mm. Al filtration, half value layer 0.9 mm. Cu. A field size of 10×10 cm. at 50 cm. target skin distance was employed and the total tumor dose was 1,000 r.

The patient made a complete recovery (Fig. 12) and a repeat roentgenographic examination done in May, 1959 was negative.

Case iv. T.V., a two and one-half year old female, complained of pain in the lower back and legs for six weeks prior to admission. The pain appeared to be relieved at complete bed rest, but not with aspirin. Roentgenograms of the lumbar spine taken in a union clinic health center were reported to be negative.

On January 28, 1954 the patient was admitted to St. Charles Hospital at which time the pain was reported to be in the lower back and right lower extremity. Physical examination at this time including complete neurologic survey was reported to be negative. Laboratory findings were negative. Tuberculin OT 1:10,000 was negative.

Roentgenographic examination on January 29, 1954 revealed an early destructive lesion of the body of L_4 (Fig. 13) which, in the absence of any significant reactive soft tissue pathology at this level, was thought to be metastatic in origin. Intravenous pyelography done on February 24, 1954 was negative. However, during this

Fig. 16. Case v. Eosinophilic granuloma in which extensive destructive change is demonstrated.

Fig. 17. Case v. One month after Figure 16, further destructive change is seen.

interval there was almost complete dissolution of the affected vertebral body (Fig. 14). The roentgen impression was that of eosinophilic granuloma.

The patient received no specific therapy except for bed rest and analgesics as needed and remained well on this regimen. Repeat roentgenograms on March 16, 1954 showed recalcification of the vertebral body. At this time we felt that the roentgen impression of eosinophilic granuloma had been confirmed. Before discharge from the hospital in May, 1954 a residual vertebra plana was demonstrated. At no time during the patient's hospitalization was there a febrile episode. The patient was discharged in May, 1954.

At the patient's last clinic visit in May, 1956 repeat roentgenograms of the lower lumbar spine revealed the presence of a healed vertebra plana (Fig. 15). The patient was completely asymptomatic at this time.

Case v. K.M., a two and one-half year old child, was admitted to St. Charles Hospital on October 5, 1949 with a history that she had been well until ten weeks prior to admission when she developed pain in the left hip. The patient was seen by a chiropractor who advised roentgenographic study. Roentgenograms of the left hip supposedly revealed "tuberculosis of the left ilium." The patient was placed in a hip spica six weeks prior to admission. In the plaster cast she was completely asymptomatic. We had the opportunity to review the roentgenograms prior to the patient's hospital admission and we felt that the roentgen findings were more consistent with a neoplastic process (Fig. 16 and 17). The patient was then admitted to the hospital and on October 6, 1949 a biopsy of the left ilium was performed.

The surgeon reported that the lesion was in juxtaposition to the left greater sciatic notch and had produced expansion of the cortex. When the cortex was entered a yellowish white gelatinous material was found. A segment of

Fig. 18. Case v. Two years and three months following surgical removal of the lesion, no residual pathology is demonstrated.

this material was removed for microscopic study. The patient had an uneventful postoperative period.

The pathologist reported the lesion to be that of an eosinophilic granuloma.

On October 18, 1949 complete curettage of the lesion was performed and again the patient had an uneventful postoperative course.

Roentgenographic survey of the osseous system following surgery failed to reveal evidence of any additional pathology. The patient was discharged from the hospital on October 28, 1949, completely asymptomatic in a plaster spica.

A clinical and roentgenologic examination in January, 1952 was negative (Fig. 18).

SUMMARY

We have attempted to review the literature in order to re-emphasize that Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma are related processes representing different phases of the same basic disease.

Occasionally, both clinically and roentgenographically, particularly after the disease is disseminated, there is such a similarity of findings that it is difficult to classify the disease under any single nosologic entity.

The prognosis in Letterer-Siwe disease and Hand-Schüller-Christian disease has improved considerably since the advent of therapy with the corticosteroids and it is suggested that this will be the treatment of choice in the disseminated phase of the disease. If therapy with corticosteroids is unsuccessful, radiomimetic drugs should be considered. Although therapy with P^{32} has never been described in this disease, it should be a consideration, particularly if, after tracer doses of P^{32}, the abnormal tissue shows a relatively selective uptake of the radioactive material. Finally, if treatment with all other modalities fails, deep roentgen therapy should be utilized with attention directed to the symptomatic foci.

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REPORT OF A CASE WITH NIEMANN-PICK DISEASE: CORRELATION OF ROENTGENOGRAPHIC AND AUTOPSY FINDINGS

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THE roentgenographic appearances of various organ systems in Niemann-Pick disease according to the many reports in the literature indicate a paucity of abnormal findings. We recently encountered a patient with infantile Niemann-Pick disease in whom the roentgenographic picture was unusual. In addition to the previously reported abnormal roentgen findings, the medullary cavities of the long bones were widened and there was thinning of the cortices and expansion of some of the shafts. The distal femurs had the Erlenmeyer flask deformity usually associated with Gaucher's disease. It may be of interest to review the roentgenographic findings of previously reported cases and to describe those noted in our case.

REPORT OF A CASE‡

The patient was the first child of Jewish parents. Pregnancy was uncomplicated and at term a 6 pound, 11 ounce male was delivered normally. At three months of age, however, hepatosplenomegaly was discovered, and at six months the infant was admitted to another hospital for diagnostic studies. A diagnosis of Niemann-Pick disease was made on the basis of a bone marrow aspiration. During the next eight months the infant was seen at three other institutions before being admitted to the City of Hope Medical Center.

Physical examination revealed a chronically ill fourteen month old boy. He had protuberant eyes and decreased subcutaneous fat. Funduscopy disclosed cherry red spots in the maculae. The abdomen appeared enlarged, and the liver was felt 9 cm. below the right costal margin and the spleen 10 cm. below the left costal margin.

‡ Detailed biochemical studies are in progress and will be reported separately by the Department of Pediatrics.

There was minimal generalized lymphadenopathy and the extremities were emaciated. Deep tendon reflexes and the cremasteric reflex were absent. There was a questionable bilateral Babinski sign.

The diagnosis of Niemann-Pick disease was confirmed when the characteristic cell was found in a marrow aspirate. Skeletal survey roentgenograms revealed generalized osteoporosis with wide medullary cavities and diffuse underconstriction of the long bones (Plate 1, 1*a*, 1*b* and 2). The expansion of the shafts of the long bones was most marked in the left humerus and both femurs. A miliary fine nodularity, which did not change appreciably during the nine months the child was followed at this institution, was noted on the chest roentgenogram (Plate 1 3). A roentgenogram of the abdomen showed hepatosplenomegaly (Plate 1 4).

The child had a progressively downhill course and died when twenty-one months old.

The pertinent autopsy findings were as follows: The patient was underdeveloped, poorly nourished, 82.5 cm. tall and weighed 10.2 kg. The scrotum and extremities were edematous. There was an eczematous skin eruption of the torso and upper arms. The peritoneal cavity contained 1,000 cc. of almost clear pale milk-colored fluid, and characteristic Niemann-Pick cells were found in the liver, spleen, lymph nodes, pulmonary alveoli, bone marrow, testes, gastric mucosa, pancreas and thymus. The brain also showed the presence of lipoid in ganglion cells and astrocytes. Lipid-laden cells in the viscera varied from 30 to 80 μ in greatest dimension. They had abundant cytoplasm, which in hematoxylin-eosin preparation was foamy with numerous smaller clear vacuoles. These cells were red when stained with Sudan IV. Their nuclei were comparatively small and slightly irregular.

Many pulmonary alveoli were filled with foamy cells (Plate II 5), and there were also foci of acute bronchopneumonia.

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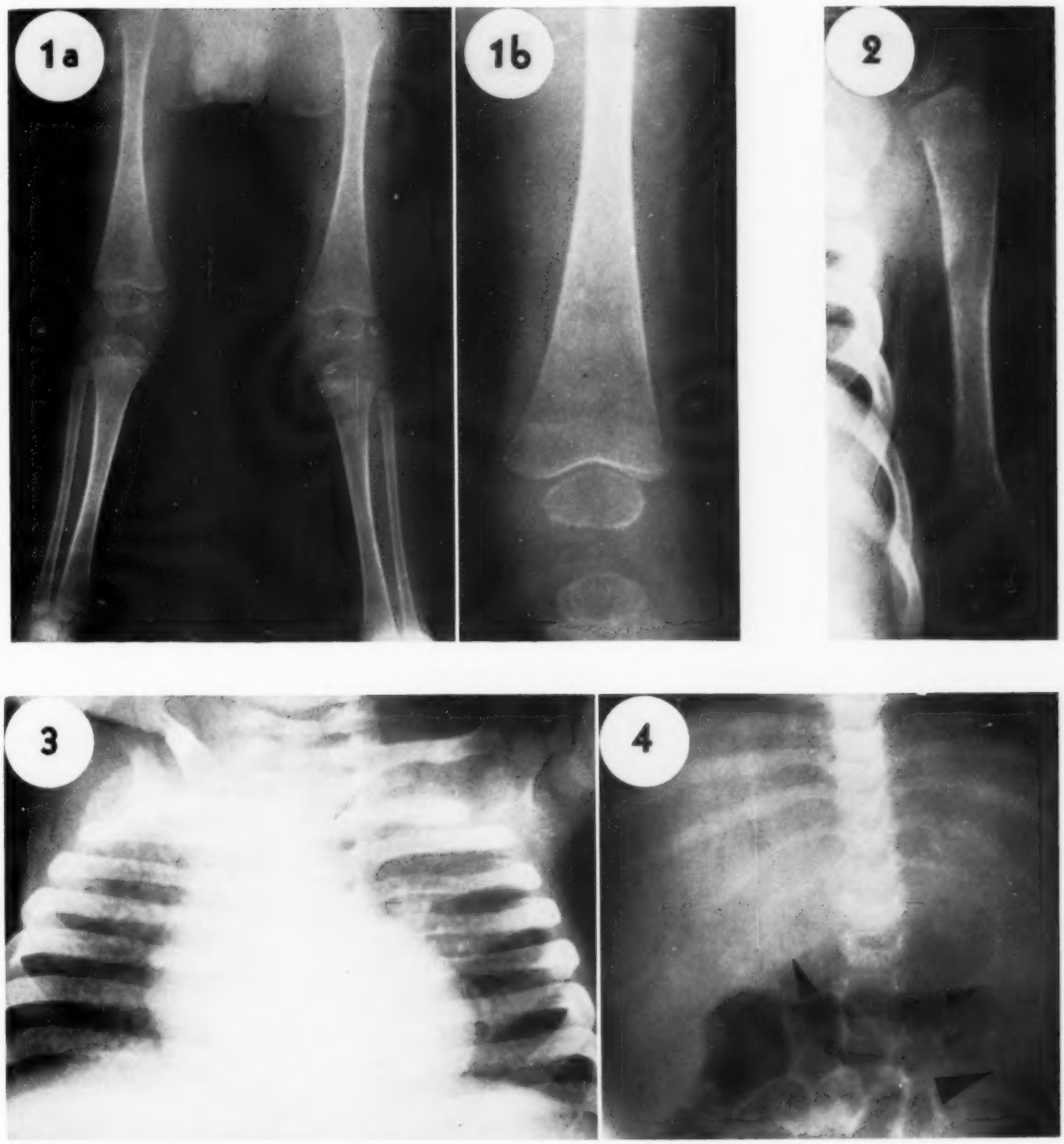

Plate I. (1*a*) Anteroposterior roentgenogram of both lower extremities shows thinning of the cortices, wide medullary spaces and diffuse underconstriction of the long bones. (1*b*) Roentgenogram shows detail of expanded distal femoral shaft. (2) Anteroposterior roentgenogram of the left upper extremity shows thinning of the cortex and expansion of the proximal half of the humerus. (3) Anteroposterior roentgenogram of the chest shows a reticulated linear pattern of markings with miliary nodularity in both lungs. (4) Arrows indicate the borders of the enlarged liver and spleen.

The liver weighed 900 gm., was very firm, and light orange-yellow. Grossly, the architectural detail was indistinct. Microscopically, the architecture was considerably distorted by great numbers of foamy cells which distended the sinusoids. Some liver cells also had a slight foamy appearance but in comparison were minimally involved (Plate II, 6*a* and 6*b*). The spleen weighed 305 gm. It had a granular surface, was firm and on sectioning was of a diffuse golden orange color. Microscopically, the spleen, thymus and lymph nodes were extensively replaced by foamy cells identical to those described above.

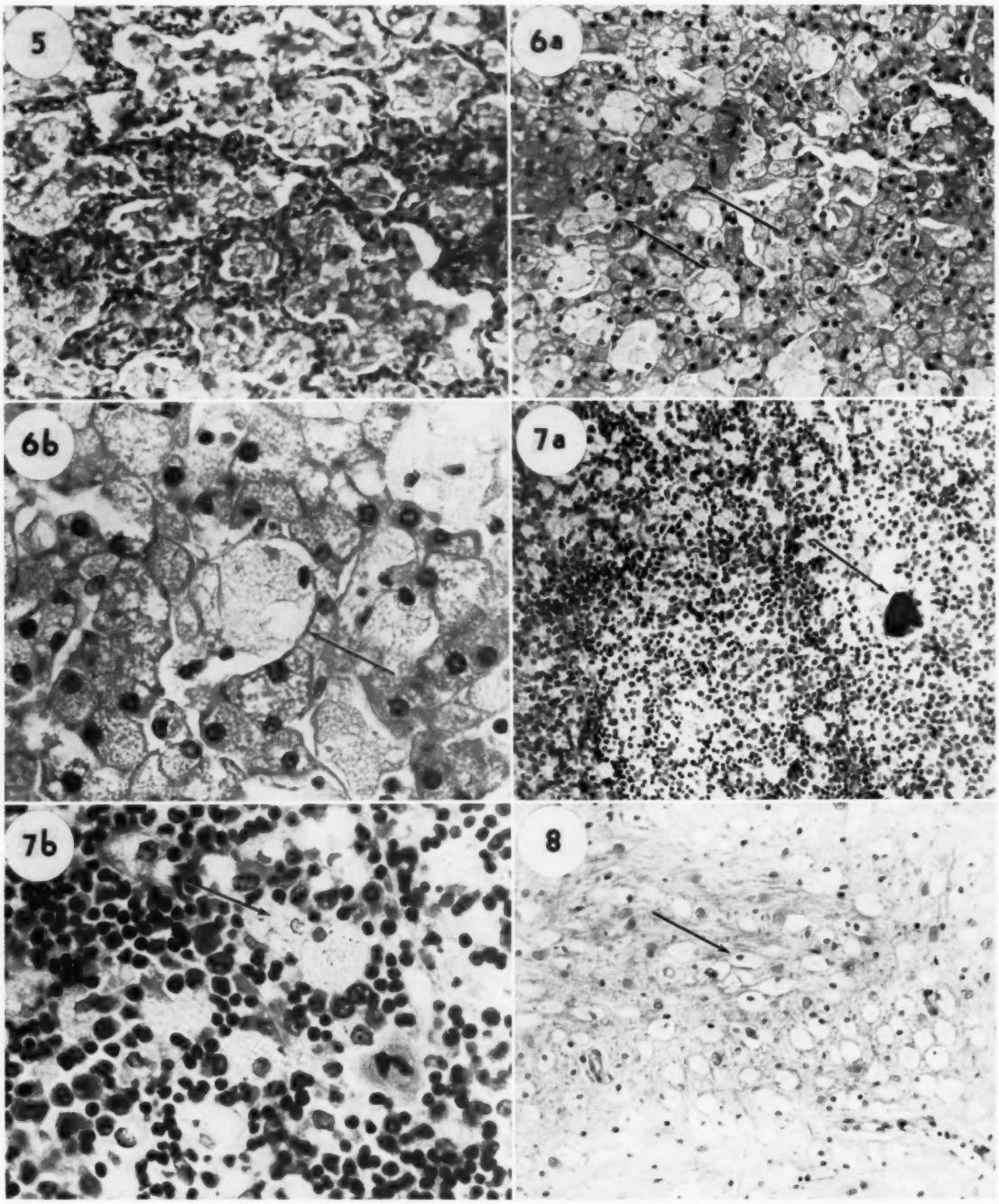

Plate II. (5) Photomicrograph of lung specimen shows numerous foamy cells within the alveoli. (*6a*) Photomicrograph of liver specimen (low magnification) shows numerous foamy cells distending sinusoids. (*6b*) Higher magnification of *6a* shows details of large lipid containing cells. (*7a*) Photomicrograph of bone marrow shows relatively small trabeculae of spongy bone amid abundant cellular marrow. (*7b*) Higher magnification of *7a* shows foamy cells admixed with hematopoietic elements. (8) Photomicrograph of brain specimen shows numerous glial cells with large amounts of clear cytoplasm.

The bone marrow was very cellular. Trabeculae of spongy bone appeared compressed and sparse within the marrow (Plate II 7*a*). In addition to cells of the hematopoietic series, the marrow spaces contained numerous foamy cells which were somewhat smaller than those in the lymph nodes, liver and spleen. Megakaryocytes and younger forms of the erythrocytic series could be identified. Mature forms were sparse (Plate II 7*b*).

The brain showed cortical atrophy of a slight to moderate degree. It weighed 998 gm. and was unusually firm. Almost all of the ganglion cells had abundant foamy cytoplasm and were approximately four times larger than the swollen glial cells, which were present in great numbers (Plate II 8).

DISCUSSION

Thannhauser[9] notes that in the infantile form of Niemann-Pick disease the skeletal system sometimes shows slight osteoporosis; however, this change was usually not found even though the bone marrow was involved. The lungs showed miliary nodules. Hepatosplenomegaly was palpable in the infants, but roentgenographic correlation was not noted. Unfortunately, in the reports of the adult form of Niemann-Pick disease reviewed by Thannhauser, there was no description of the roentgenographic appearance of the bones.

Brailsford[3] simply states thst no definite bone changes are seen. Schinz *et al.*[8] also are of the opinion that bones in Niemann-Pick disease show no gross roentgen changes. Caffey[4] comments that the patient with Niemann-Pick disease usually dies before there are any conspicuous skeletal changes. Poncher[7] reported a case of an eighteen month old patient whose tubular bones showed areas of rarefaction.

Baumann *et al.*[2] published a comprehensive review of the literature as well as a report on their own detailed studies of an additional case of Niemann-Pick disease. They observed miliary infiltration of the lungs and osteoporosis of the skeletal system on the roentgenograms of their patient, which were the only abnormalities they encountered. The bone age appeared somewhat accelerated; there were three carpal ossification centers in the wrists at eighteen months of age.

In his review article, Van Creveld[10] states that the roentgenograms of the long bones in Niemann-Pick disease often demonstrate osteomalacia and osteoporosis. He also refers to Freudenberg's[6] report of a spontaneous fracture, which actually deals with a set of twins, both of whom had Niemann-Pick disease. Their bones showed a delay in appearance of growth centers in the wrists, were abnormally radiolucent, lacked a well defined cortex and had a coarsened trabecular pattern. Initially, there was no sign of rickets and the condition was not present in the first twin, who died at the age of seventeen months. However, in the second twin, shortly before he died fourteen months later, a transverse fracture without displacement involving the left femur was found and yet there was no history of antecedent trauma. The roentgenograms also demonstrated florid rickets. Freudenberg postulated that the combination of severe osteoporosis and superimposed rickets had led to the spontaneous fracture. There are no other case reports of fractures in patients with Niemann-Pick disease. Incidentally, there were no pulmonary abnormalities, and abdominal roentgenograms were not mentioned in Freudenberg's report.

Videbaek[11] described a case of a five and one-half year old boy followed for over three years after Niemann-Pick disease was diagnosed. There was roentgenographic evidence of osteomalacia and delayed bone development as well as diffuse speckled and lacy infiltration of both lung fields.

The infant with Niemann-Pick disease reported by Alexander[1] had the unusual finding of extensive symmetric calcification in the adrenal glands. The adrenals were enlarged due to the presence of abnormal lipoid deposits in abundant vacuolated cells. Although Alexander suggested a causal relationship of the lipoid deposits and the calcification, it is also possible that the finding was coincidental since it has not

been noted in any other reported case of Niemann-Pick disease.

Crocker and Farber[5] have reviewed the roentgen findings in their 18 cases, ranging in age from newborn to 19.6 years. They found no abnormalities on many skull roentgenograms, intravenous pyelograms and gastrointestinal studies. Their patients often had miliary infiltrates in the lungs appearing as early as at the age of four months. These usually did not change after they were first detected. At autopsy the infiltrates consisted of numerous foam cells in alveolar spaces. The bones frequently showed coarsened trabecular patterns, widened medullary cavities and undermineralization. One patient showed these changes early, but later in life the bones apparently returned to normal. There was occasional mild failure of tubulation but none of the cases showed the Erlenmeyer flask deformity characteristic of Gaucher's disease.

Our patient had hepatosplenomegaly as demonstrated on a plain roentgenogram of the abdomen and miliary nodular infiltrates in the lungs. The numerous foamy histiocytes in the liver, spleen and pulmonary alveoli found at autopsy accounted for the roentgen abnormalities. The appearance of the bones was due to replacement of normal marrow hematopoietic elements by foam cells which seemed to compress the bony trabeculae and also ballooned out the cortices of the long bones.

SUMMARY

A case of Niemann-Pick disease is presented and the roentgen and autopsy findings in the bones, lungs, and abdomen are discussed. A review of the literature is also presented relative to the roentgenographic findings.

In addition to widened medullary cavities, undermineralization of bones and mild failure of tubulation reported by others, our patient had a more marked diffuse underconstriction of the long bones as well as expansion of the shafts of some of these bones.

An abdominal roentgenogram verified the clinically palpable hepatosplenomegaly.

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Vol. 85, No. 4

GAUCHER'S DISEASE

CLINICAL AND ROENTGENOLOGIC MANIFESTATIONS

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GAUCHER'S disease, originally described as an epithelioma of the spleen, is now generally accepted as being a hereditary metabolic disorder characterized by the accumulation of various cerebrosides in the reticuloendothelial organs, especially the spleen, liver, and bone marrow.

The disease, though uncommon, is by no means rare. The great majority of cases reported have been in Jews though various other ethnic and nationality groups may be affected. Relatively few cases have been reported in Negroes and Orientals. Males and females are affected in about equal numbers. There have been a number of cases occurring in siblings; in only a few cases, however, has the disease been found in a parent and child. Hsia *et al.*[13] suggest that there are three genetically distinct groups of Gaucher's disease: (1) in a few instances the gene is transmitted as an autosomal dominant; (2) in most instances the gene is transmitted as an autosomal recessive; (3) in a small group of cases in which there is neurologic involvement in addition to the more common bone, liver, and spleen changes, it also appears that the gene is transmitted as an autosomal recessive.

The lipoprotein storage and metabolism in Gaucher's disease have been extensively studied. At one time it was the general belief that a galactocerebroside, kerasin, was the chemical stored in the liver, spleen, and other viscera. It is now known that either glucocerebrosides, galactocerebrosides, or both, may be the lipoproteins stored, with behenic acid the major fatty acid constituent.[23] These substances are not normally found in the liver or spleen nor are they carried to these organs and deposited. Rather it appears that there is probably an enzymic abnormality causing an accumulation of cerebrosides in the reticulum cells.[20,28]

The involved organs contain varying numbers of "Gaucher's cells," which are thought to be abnormal reticulum cells. The Gaucher cell is a large polyhedral or round cell measuring 20 to 80 μ in diameter. Its nucleus is small and eccentrically placed. Most often there are multiple nuclei, as many as twenty. The pale-staining cytoplasm has a wrinkled tissue paper appearance (Fig. 1). The cell degenerates slowly and it does not undergo mitotic

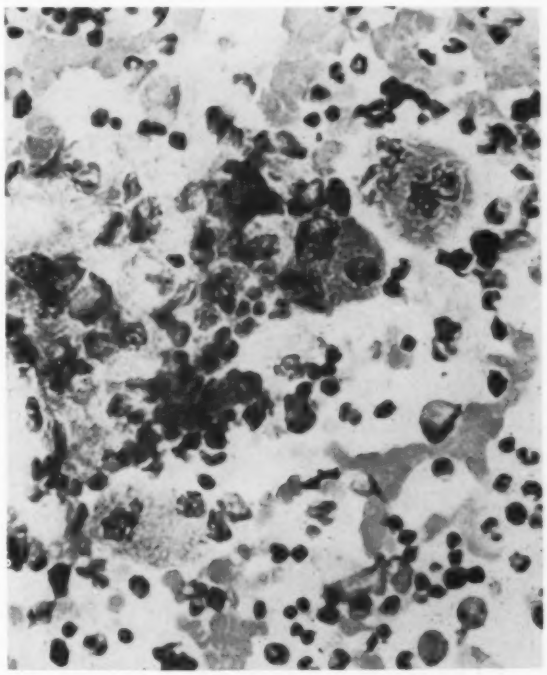

FIG. 1. Bone marrow smear (Wright's stain, ×375). The Gaucher cells are large and multinucleated. The cytoplasm is light staining with a crinkled or punctate appearance.

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division. The spleen, liver, and bone marrow may be packed with these cells which may displace the normal cellular elements. Lymph nodes are often similarly involved, particularly the mesenteric and other deep-lying groups. The superficial lymph nodes are uncommonly involved and the mediastinal lymph nodes rarely so. The central nervous system, the lungs, and other viscera may also be infiltrated with these cells.

CLINICAL FEATURES

Clinically, Gaucher's disease presents in two general forms, the adult and the infantile. The adult form is by far the more common.

ADULT FORM

In the typical case the patient presents with hepatomegaly and splenomegaly, the latter the more prominent. The spleen is often enlarged to tremendous proportions; those weighing 5 to 6 kg. are not rare and one weighing over 8 kg. has been reported.[12] In view of this it is surprising that splenic rupture is rarely encountered.[14] On occasion there is no hepatomegaly or splenomegaly in spite of varying degrees of bone involvement. The patient usually complains of weakness and fatigability. Mild to moderate normochromic or hypochromic anemia, leukopenia, and thrombocytopenia may be present and there may be resultant petechial hemorrhages and even epistaxis and gastrointestinal bleeding. Rarely, there may be thrombocytopenia without associated anemia or leukopenia.[6] There has been a report of one case of Gaucher's disease with macrocytic normochromic anemia with leukopenia.[9] Infrequently, there is enlargement of cervical, axillary, or inguinal lymph nodes. Pingueculae, areas of wedge-shaped yellowish-brown pigmentation of the conjunctivae adjacent to the pupils, may be present. Deep yellowish skin pigmentation may likewise appear, especially on the lower extremities. The pingueculae and lower extremity pigmentation are considered to be near-pathognomonic of Gaucher's disease.[3,11] The conjunctival and skin changes apparently reflect a generalized hemachromatosis and have been known to disappear following splenectomy.[15] A high

Fig. 2. Case 1. Composite roentgenogram of abdomen and gallbladder showing marked splenomegaly and cholelithiasis.

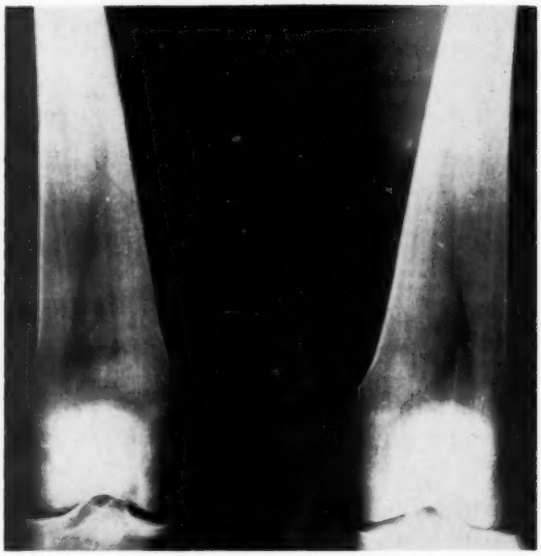

Fig. 3. Case 1. The distal ends of the femora show typical underconstriction and cortical thinning (Erlenmeyer flask appearance).

Fig. 4. Case II. There is bilateral femoral head destruction but the patient has almost no discomfort or gait disturbance.

incidence of myopia and malar flush has been reported.[3] An acquired hemolytic jaundice may be present; this may account for the occasional case of gallstones encountered among even young adults with Gaucher's disease.

Though the liver is frequently involved in Gaucher's disease, abnormalities of liver function are rare. Elevation of the serum bilirubin and delayed excretion of bromsulphalein are the most common abnormalities found. In one reported case marked ascites was present; this was secondary to extensive parenchymal infiltration of the liver by Gaucher's cells.[18]

The bone marrow is frequently infiltrated with Gaucher's cells and depending on the site and degree of infiltration the patient may or may not have symptoms. At times there is localized bone pain which may be severe enough to mimic osteomyelitis and many patients have been operated on because of this mistaken diagnosis.[5,7,9,16,26,30] Draznin and Singer[7] have stressed the importance of recognizing these "bone crises" so as to avoid needless surgery. Strickland[24] noted that when patients with Gaucher's disease are operated upon because of a mistaken diagnosis of osteomyelitis, a sinus may form which is particularly intractable and may last for weeks.[24]

Spontaneous fractures of long bones or of vertebrae may occur. Deformity of the femoral heads much like that seen in aseptic necrosis (Calvé-Legg-Perthes disease) may result from bone weakening or infarc-

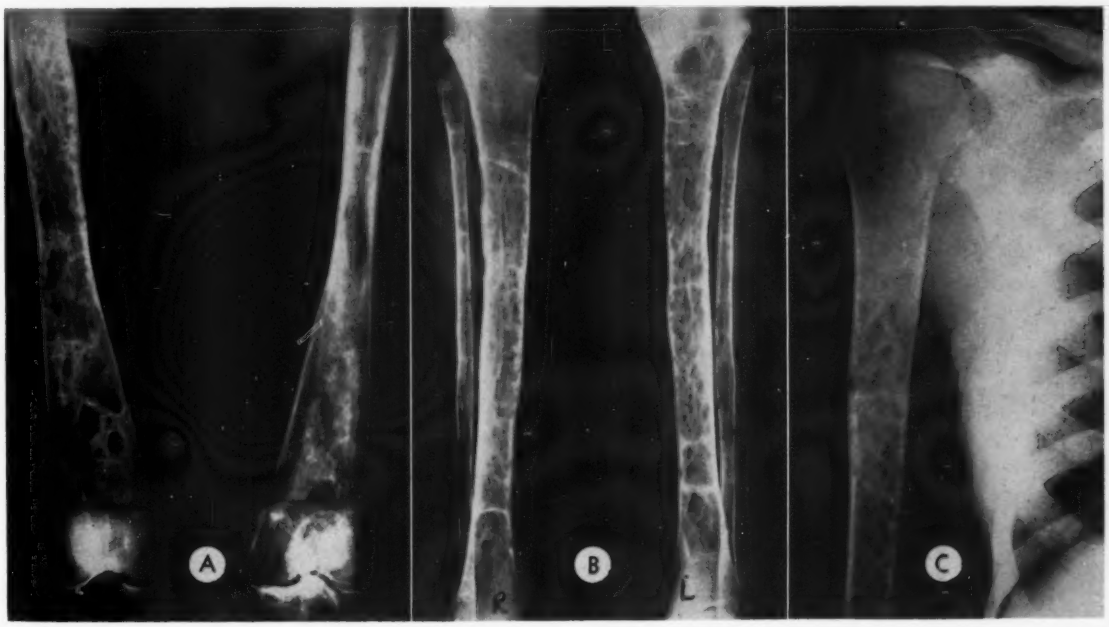

Fig. 5. Case II. (*A*) Femora; (*B*) tibiae; (*C*) humerus. There is extensive replacement of normal bone by Gaucher's cells, with a cyst-like appearance. In some areas the cortex is markedly thinned and there is irregularity of gross bone contour. The femora are appreciably underconstricted.

Fig. 6. Case II. The bones of the forearms and metacarpals show the same disruption of normal architecture as do the other long bones.

tion. Deformities of varying degrees may result from weakening of the bones secondary to marrow replacement by the abnormal cells. The skull is rarely involved; in fact, the author has found only one case report in which the skull was a proved focus of Gaucher's disease, the diploë being extensively infiltrated with Gaucher's cells.[21] This was a postmortem finding; there was no mention of skull roentgenograms. In a few cases infiltration of the posterior lobe of the pituitary gland has been found. It has been postulated that this portion of the pituitary gland is related to the reticuloendothelial system.[15]

Occasional cases have been reported in the literature and encountered by the author in which the patient has had no hepatomegaly, splenomegaly, or roentgenologic evidence of bone involvement. The diagnosis had been made on bone marrow aspiration performed to seek out the cause for anemia.

It is of interest that elevation of the serum acid phosphatase may be found with Gaucher's disease.[29] The cause for this is as yet unknown. This is not related to the degree of roentgenographically demonstrated bone involvement and may be found in both males and females.

Earlier reports indicated that spontaneous abortions, sterility, and postpartum hemorrhage are common in Gaucher's disease. More recently this concept has been refuted.[4,13,27]

The diagnosis is made by a finding of Gaucher's cells in the bone marrow, spleen, liver, or lymph nodes. The cells are not found in the peripheral blood nor are there biochemical changes in the peripheral blood which may aid in the diagnosis.

There is no known effective treatment. Splenectomy may be performed to overcome symptoms due to hemolytic anemia

Fig. 7. Case II. The body of the ninth vertebra is slightly compressed. There has been no history of trauma or back pain. In some cases vertebral compression may be severe enough to cause a gibbus.

or thrombocytopenia, or to relieve the discomfort attendant upon carrying a huge spleen. It is no longer felt that splenectomy increases the resistance of the patient with Gaucher's disease to infection nor does it halt the progression of skeletal involvement. Roentgen irradiation of the spleen does not retard its growth or otherwise influence the course of the disease. Persons with the adult form of Gaucher's disease may live into the sixth or seventh decades but most often they die by the time they reach forty years, death being due to hemorrhage or intercurrent infection.

Fig. 8. Case III. Roentgenogram of a child six years old. The deformity of the right femoral neck is secondary to an old fracture. This might also account for the bone sclerosis in the area. The architecture of the left femoral neck suggests Gaucher cell infiltration.

INFANTILE FORM

In this form of Gaucher's disease signs and symptoms may appear within the first few months of life. Anorexia and lassitude are early symptoms and retardation of physical and intellectual development often occurs. In the cases reported accumulation of oral and pharyngeal mucus has been a serious problem. Hypertonicity and opisthotonus are prominent features. The abdomen becomes distended because of progressive hepatosplenomegaly. Pancytopenia of varying degree is invariably pres-

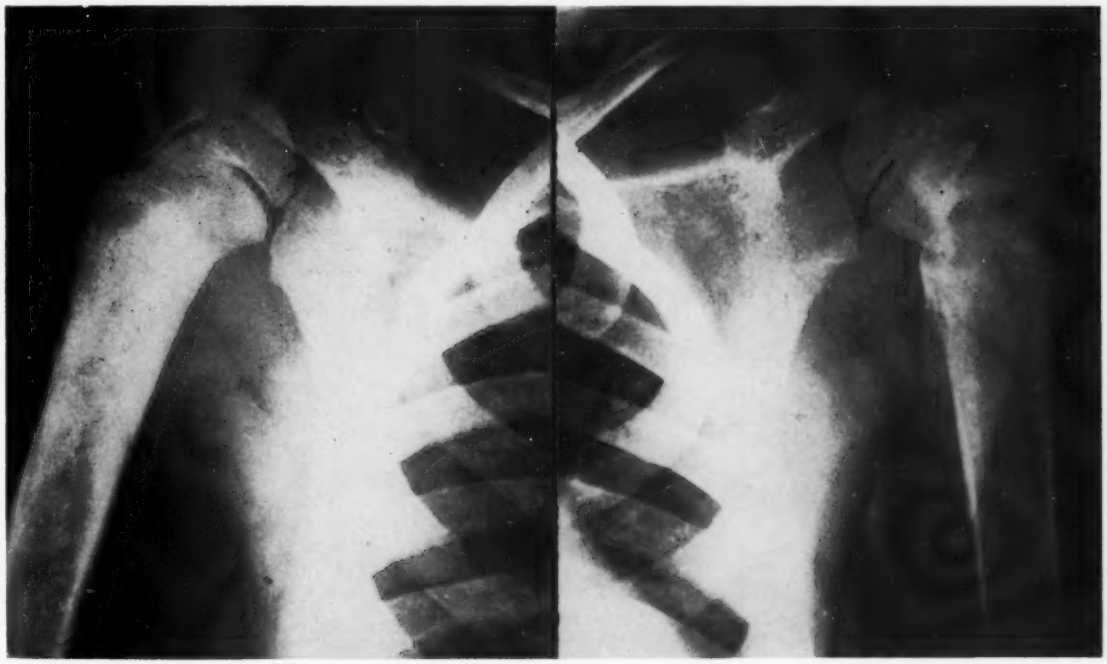

Fig. 9. Case III. Roentgenograms made at the age of six years. The neck of the left humerus is deformed, secondary to a healing pathologic fracture. The upper portion of the shaft of the right humerus is sclerotic; there had never been a fracture in this region.

Fig. 10. Case III. Roentgenogram made at the age of four years. There is marked underconstriction of both femora and marked cortical thinning. Similar though less striking changes are present in the tibiae.

ent. Skin and conjunctival pigmentation does not occur in infants or children afflicted with Gaucher's disease. Death usually occurs in the second year.

The Gaucher cell infiltration in bone, liver, spleen, and lymph nodes is the same as in the adult form. Unlike in the adult form, however, is the frequent pulmonary infiltration. The alveolar walls, alveoli, and bronchi often contain large numbers of Gaucher's cells and it has been suggested that an examination of the sputum for these cells might easily lead to an antemortem diagnosis and obviate the need for splenic or bone puncture.[8,22] (It is of interest that in one report of a case of Gaucher's disease in childhood with mediastinal and pulmonary infiltration the sputum was examined about twenty times for Gaucher's cells but the result was always negative.[19]) In the infantile form the central nervous system is one site of involvement which is not found in the adult form. The brain has been reported as showing atrophy, vacuolization and mummification of the medium-sized pyramidal cells of the cerebral cortex.[22] This is of a nonspecific nature, being found in a wide variety of acute nonspecific encephalopathies of infants and children. In some cases Gaucher's cells have been found in an adventitial reaction about cerebral blood vessels.[2]

ROENTGENOLOGIC APPEARANCES

From the clinical and pathologic appearances one would expect the roentgenologic findings to be many and varied; this is indeed the case. The bony structures are those subject to the broadest spectrum of roentgenographically demonstrable changes; the abdominal and thoracic viscera exhibit less spectacular and less specific changes.

Bones. The roentgen changes in the bones are dependent upon and reflect the degree of marrow infiltration and replacement by Gaucher's cells. One of the more common findings is expansion of the long bones with variable degrees of cortical thinning. This is best recognized at the distal end of the shaft of the femur but may also be quite evident elsewhere (Fig. 3; 5, *A–C*; and 10).

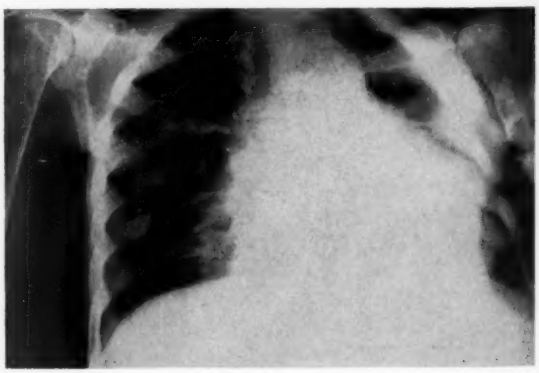

Fig. 11. Case IV. Chest roentgenogram shows marked deformity of the humeri. The ribs are also thinned, presumably due to Gaucher cell infiltration.

The normally present concavity is erased and there may be localized bulging of contour. This has been aptly described as giving an Erlenmeyer flask appearance (Fig. 3). This finding is not specific for Gaucher's disease but may also be found in the hemolytic anemias (especially thalassemia), leukemia, healed rickets, hyperthyroidism, old healed fractures, and Albers-Schönberg disease. However, because of the many other clinical and roentgenologic signs in these diseases the differential diagnosis does not pose a serious problem. The replacement of normal medullary bone and subsequent cortical thinning may weaken the bone structure sufficiently to cause pathologic fractures. These are usually not delayed in healing but may leave significant deformity (Fig. 8 and 9). In long bones the appearance may be one of numerous sharply circumscribed round radiolucent defects not unlike the patterns found in metastatic cancer, multiple myeloma, or osteitis fibrosa cystica (Fig. 5, *A–C*; 6; 11; and 12). Associated with this appearance there may be irregular expansion of gross bone outline. It has been stated that periosteal reaction does not occur in Gaucher's disease. The more recent reports, however, disprove this concept.[7,24] The periosteal elevation does not have any specific roentgenographic appearance. Strickland's[24] cases had both lace-like and layer patterns. In some patients the bone marrow may become fibrotic and give a myelosclerotic roentgen appearance (Fig. 8, 9, 12 and 13). Whether the sclerosis is due to direct osseous metaplasia of reticular and collagen fibers[31] or to bone repair secondary to destruction[10] has as yet not been proved.

The tubular bones of the hands and feet are rarely sufficiently involved to show altered roentgenographic changes. Articulating cartilage is not invaded by Gaucher's cells and thus arthritic changes are not seen except secondary to destruction of paraarticular bone.

Destruction of the head of the femur is a relatively common occurrence in Gaucher's disease and may present an appearance much like that seen in Calvé-Legg-Perthes

Fig. 12. Case IV. There is irregular expansion of the right femur with a pseudocystic appearance. The femoral head and neck and adjacent pelvic bones are sclerotic. The stump of the left femur (amputated four years previously) also shows bone sclerosis.

Fig. 13. Case V. The head of the humerus is flattened, irregular in contour, and somewhat sclerotic. Biopsy was positive for Gaucher's disease. There was no history of trauma. Intermittent shoulder pain had been present for two years. (The apparent destruction of the clavicle and acromion is a photographic artefact.)

Fig. 14. Case VI. Roentgenogram of the abdomen shows the classic Gaucher's triad: splenomegaly, cholelithiasis (barely discernible in the reproduction), and femoral head destruction.

disease (Fig. 4 and 14). The onset of this complication may occur at any age. One patient in the present series had similar changes in the head of the humerus (Fig. 13). Like in Calvé-Legg-Perthes disease, there may be reconstitution of the affected bone though this is probably an uncommon occurrence in Gaucher's disease.[1] The deformities are due to replacement of normal bone by Gaucher's cells rather than to vascular deficiency (infarction) as is postulated for some cases of Calvé-Legg-Perthes disease. Other bone or soft tissue infarcts are not seen in Gaucher's disease.

There have been no conclusive reports of roentgenographic visualization of cranial or facial bone involvement nor has the author encountered any such change. Fairbank[8] noted that one case showed "fine mottling" of the cranial bones, certainly a nonspecific and not necessarily abnormal pattern. Morgans[17] reported a patient who had some long bone changes and also "a small radiolucency in the left parietal bone."

Viscera. Splenomegaly may vary from slight to extreme. Hepatomegaly is generally less evident than splenomegaly. There is an increased incidence of gallbladder stones, presumably secondary to an acquired hemolytic anemia (Fig. 2 and 14). Ascites may rarely occur. The gastrointestinal tract does not become sufficiently infiltrated by Gaucher's cells to permit roentgenologic recognition. Displacement by the enlarged liver and spleen are generally the only positive roentgen findings.

The lungs, when involved, have a mottled appearance, generally throughout both lung fields (Fig. 16). Though some authors mention the spread from mediastinal lymph nodes to the pulmonary parenchyma, mediastinal lymphadenopathy is not evident on roentgenograms. Neither atelectasis, pneumothorax, nor pleural effusion has been reported.

Though renal infiltration has been found in Gaucher's disease,[12] this is only a histologic finding; roentgenographic demonstration of such kidney changes is as yet unreported.

It should be remembered that not in all cases are there positive roentgenographic findings. There may be no demonstrable splenomegaly, hepatomegaly, or bone involvement in patients with Gaucher's disease who do have the hematologic changes. In these cases the disease is probably less severe than in those with roentgenologically demonstrable lesions.

REPORT OF CASES

A small number of case histories are presented to illustrate the many and varied clinical and roentgenologic manifestations of Gaucher's disease.

Case 1. R.R. This Jewish male was well until about the age of nineteen years. At that time he became aware of a left upper quadrant mass and easy fatigability. He was found to have marked splenomegaly and moderate pancytopenia. Roentgenographic studies confirmed the splenomegaly and also revealed gallbladder stones (Fig. 2). This combination suggested Gaucher's disease. Roentgenograms of the femora further

Fig. 15. Case vii. (*A*) December 8, 1952: The femora show no abnormality. (*B*) February 16, 1954: There are foci of normal bone replacement in the left femoral head and in both femoral shafts.

supported this diagnosis (Fig. 3), and bone marrow aspiration confirmed it. Because of hemolytic anemia, upper abdominal discomfort, and hemorrhagic tendencies (i.e., petechiae and prolonged bleeding following tooth extraction) splenectomy was performed in 1957 when he was twenty-nine years old. The spleen weighed 2,610 gm. (normal, 100–180 gm.). There has been no untoward bleeding since then and there has been moderate improvement in the anemia.

Case ii. B.B.G. (This case has been reported previously by Draznin and Singer.[7]) This Jewish female was diagnosed as having Gaucher's disease at the age of five years. At that time she had hepatosplenomegaly, pallor, and episodes of hematuria and epistaxis. She had brownish pigmentation of the skin, cervical, axillary, and inguinal lymphadenopathy, and marked pancytopenia. The diagnosis was made by splenic puncture. Splenectomy was then performed; the spleen weighed 570 gm. (normal, 100–180 gm.). Since then (the patient is now thirty-five years old) she has been free of purpura and has had no complaints which could be in any manner attributed to Gaucher's disease except for some recurrent pain and tenderness over different bones and joints. Twice she was operated on with the diagnosis of osteomyelitis. At neither time was osteomyelitis found. The initial roentgenograms were negative but follow-up studies showed extensive and progressive deformity of bone resulting from marrow replacement by Gaucher's cells (Fig. 4 to 7). The hemogram was within normal limits. The patient is married and has had an uncomplicated pregnancy delivering a normal son with no stigma of Gaucher's disease.

Case iii. I.R. This Jewish boy was first noted to bruise easily at the age of two months. Because one paternal uncle had known Gaucher's disease (Case 1) and another had died at the age of four years, six months after splenectomy, the child was suspected of suffering from the same affliction. This was confirmed by marrow biopsy. There developed progressively increasing hepatosplenomegaly, mild axillary and

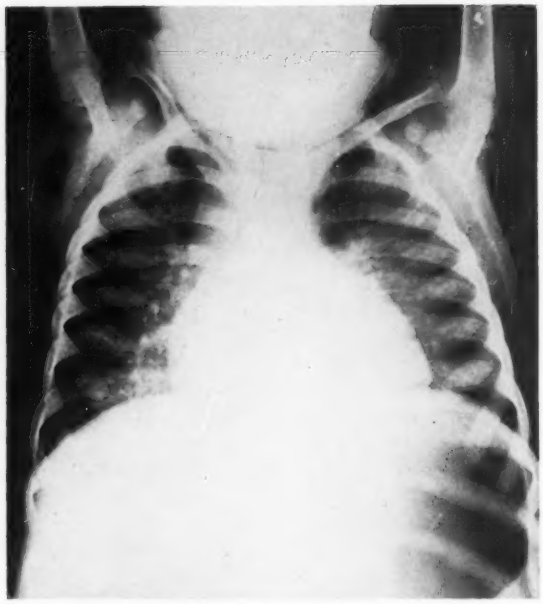

Fig. 16. Case vii. Chest roentgenogram made post splenectomy when the child was free of respiratory symptoms shows bilateral nodular and patchy pulmonary infiltration, apparently confined to the central lung zones.

inguinal lymphadenopathy, and moderate pancytopenia. The child suffered from recurrent mild episodes of epistaxis, starting at about three years. At the age of three and one-half years a splenectomy was performed; the spleen weighed 538 gm. (normal, 37 gm.). Following this the blood findings improved and there were no further manifestations of bleeding. The child, however, showed roentgen evidence of progressive replacement of bone. He has suffered from multiple pathologic fractures, some of which have healed with residual deformity (Fig. 8 to 10). He is now eight years old and is seriously limited in his activity because of his bone fragility.

Case iv. N.F. This Jewish male was first admitted to Michael Reese Hospital at the age of fifty years. He had had pain in both legs for about fifteen years which had been diagnosed as sciatica. About nine years prior to admission he fractured the left femur. After five years of treatment failed to effect satisfactory union, a high amputation was performed. At that time he was diagnosed as having Hand-Schüller-Christian disease. About four months prior to admission, he developed ascites for which he was treated at another hospital. At this time Gaucher's disease was diagnosed on bone marrow aspiration. On admission to Michael Reese Hospital, the patient was emaciated and lethargic. The skin had a yellowish-brown hue and pingueculae were present. The blood count revealed 2,300,000 red blood cells, 1,300 white blood cells, and 120,000 platelets per $mm.^3$. Roentgenograms demonstrated pseudocystic changes in the humeri and right femur as well as sclerosis of the head and neck of both femora and acetabula (Fig. 11 and 12). Splenectomy was being performed when the patient died suddenly on the operating table. Postmortem examination revealed classic Gaucher cell infiltration in a 3,000 gm. spleen (normal, 100–180 gm.) and a 2,950 gm. liver (normal, 1,500–1,800 gm.). There was lymphocytic portal infiltration but no hepatic cirrhosis.

Case v. M.M. This thiry-four year old Jewish man was admitted to the hospital because of left shoulder pain, recurrent for two years and of increasing severity for a period of three weeks. There was no history of trauma. Nine years previously, at another hospital, he had had a splenectomy because of anemia and splenomegaly. The pathologic findings were at that time unavailable. The only positive finding on physical examination was limitation of left shoulder motion. The red blood cell, white blood cell, and platelet counts were normal. Roentgen examination of the left shoulder (Fig. 13) revealed the articulating surface of the head of the humerus to be flattened, the head widened and the subarticular bone sclerotic. The cartilage space of the shoulder joint was intact.

Biopsy of the head of the humerus revealed Gaucher cell infiltration. It was later confirmed that the splenectomy was performed for this reason.

Case vi. S.L. This fifty-eight year old Jewish male was known to have splenomegaly for about seven years. Bone marrow aspiration was positive for Gaucher's disease. He had numerous small brown pigmented areas on both legs. There was moderate normocytic anemia, marked leukopenia, and slight thrombocytopenia. For a few years the patient had suffered from recurrent left hip pain. Roentgenograms revealed gallbladder stones, marked splenomegaly, and destruction of the head of the left femur (Fig. 14).

Case vii. S.M. This white non-Jewish male was diagnosed as having Gaucher's disease at

the age of seven months following study for hepatosplenomegaly and anemia. Splenectomy was performed at twenty months of age because of anemia, thrombocytopenia, and dyspnea. The spleen weighed 930 gm. (normal, 33 gm.). This was followed by some improvement in the blood picture and relief of the dyspnea. Roentgenograms revealed progressive bone replacement in the head of the left femur and in both femoral shafts (Fig. 15, *A* and *B*). At no time did the child give evidence of bone or joint pain. Chest roentgenograms showed bilateral diffuse pulmonary infiltration, most evident in the central lung fields, and punctate and nodular in character (Fig. 16). At the age of three years he had a massive hemoptysis and died one hour later. Postmortem examination revealed the liver to be cream-colored and enlarged to 1,530 gm. (normal, 418 gm.). Both lungs showed extensive lymphangiectasis on all surfaces. There were numerous Gaucher's cells in the lungs, liver, and regional lymph nodes as well as in the lumina of the smaller vessels of the brain.

SUMMARY

The many and varied clinical and roentgen manifestations of Gaucher's disease are discussed and representative roentgenograms are reproduced.

The disease may be present at all ages and may involve various organ systems.

Similarly, the disease may be a rapidly fatal one or a chronic one with few symptoms and the patient living with his disease for many decades.

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AGENESIS OF THE SACRUM AND COCCYX*

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AGENESIS of the sacrum and coccyx is an uncommon developmental abnormality of the spine. Congenital absence of the lumbar spine is more unusual, and congenital absence of the vertebral column cephalad to the tenth thoracic segment apparently is incompatible with fetal development.

Freedman,[2] in 1950, described a case of absence of the sacrum below the second sacral segment. He made a comprehensive survey of the literature pertaining to congenital absence of the lower spine and classified the 44 cases recorded since the condition was first described by Hohl in 1852. Pirkey and Purcell[3] reported in the radiologic literature 2 cases of agenesis of the lumbar and sacral vertebrae. Blumel, Evans, and Eggers,[1] in 1959, reviewed the literature and included 5 more cases from published articles. They made an intensive statistical compilation and genetic analysis of 50 additional cases obtained from a survey of one hundred Texas hospitals and three hundred orthopedic surgeons in the United States and Hawaii. A total of about 100 cases of agenesis of the lower spine has been recorded.

REPORT OF A CASE

J.L., a white female, was born three weeks prematurely on June 24, 1952. Her birth weight was five pounds and four ounces. Bowel movements were difficult from birth, and she was treated for rectal stenosis by dilatation during the first few weeks of life. An upper gastrointestinal series at the age of six months was negative. Deformity of the lower extremities was treated by applications of plaster casts during the first year. She ate very little and her weight at the age of three years was eighteen pounds. Bowel movements were irregular and often resulted in fecal impactions which required manual removal by the mother. Cathartics did not aid the bowel movements. There was incontinence. A cystoscopic examination made at the time of a urinary tract infection showed extensive cystitis throughout the trigone of the bladder.

Physical examination at the age of five and one-half years revealed underdevelopment with diminished muscular strength of both lower extremities and marked atrophy below the knees. The child's height was thirty-seven inches and her weight was twenty-five pounds. The feet were severely pronated, with the heels in a valgus position, and the toes were turned up. There was painless and full range of hip motion. She walked with a bowlegged gait swinging the pelvis in unison with the step.

There was a soft tissue mass over the lower lumbar area, and there were peculiar oblique skin creases. The pelvis was small. The rectal sphincter showed very little tone; however, there was no anesthesia of the perianal region to a pin prick.

The mental development was not impaired. One sibling had a minor foot abnormality which responded to treatment. Two other siblings and the parents are normal.

Roentgenograms showed a congenital absence of the sacral and coccygeal segments of the spine, except for a small malformed portion of the posterior vertebral arch of the first sacral segment (Fig. 1). There was a slight deformity of the inferior posterior corner of the body of the fifth lumbar segment and a wide pseudojoint space, bilaterally, between the iliac bone and the inferior part of the fifth lumbar vertebra (Fig. 2). The pelvic ring, normal in configuration at six months of age (Fig. 3), became narrowed, elongated, and slightly asymmetric with weight bearing (Fig. 4). The iliac bones approached the midline. The hip joints were normal. The twelfth rib was hypoplastic on the right. The cervical and thoracic segments of the spine were normal. The bones of the lower extremities were normal except for malposition of the bones of the feet due to soft tissue deformity.

An intravenous pyelogram showed minimal

* From the X-Ray Department of the Ferguson-Droste-Ferguson Hospital, Grand Rapids, Michigan.

Fig. 1. Lateral roentgenogram of the pelvis at the age of five and one half years. There is only a small part of the posterior arch of S-1 present. L-5 is deformed to conform with the bony mass of S-1. The remainder of the sacrum and the entire coccyx is absent.

pyelectasis and calycectasis, and enlargement of the urinary bladder.

At seven and one-half years of age she is still having difficulty with bladder and bowel control but is improving. The club foot deformity is being treated by exercises and corrective orthopedic shoes.

DISCUSSION

In congenital absence of the lower spine, the lower extremities, especially below the knees, are tapered because of muscular deficiencies and underdevelopment. An attitude of external rotation and partial flexion is common. Some type of club foot deformity is usually present. Walking is often awkward and may be impossible in the more severe cases. There is a prominence over the lumbar area. The intergluteal fold characteristically is short and the buttocks are small and flattened.

Deficiencies of the lower spinal nerves are frequent with impaired innervation to the perineum (S-2 to S-5) and the legs and buttocks (L-5 to S-1). The thigh muscles (L-2 to L-4) are usually normal if the anomaly is no more extensive than absence of the sacrum and coccyx. Most of these cases have incontinence of urine. The anal sphincter is

Fig. 2. Oblique roentgenogram of the pelvis at the age of five and one half years. There is malformation of the body of L-5 and a wide pseudo-joint space between L-5 and the ilium.

atonic, but fecal incontinence is unusual. Sometimes there are sensory nerve changes of the lower extremities, but these changes are less pronounced than motor nerve alterations.

The structural supporting pelvic ring is intact and has an essentially normal contour if the first sacral segment is present, or if there is sacralization of the fifth lumbar vertebra. When this is the case, stance and gait are almost normal. Absence of this bony "keystone" results in a vertical position of the innominate bones, which meet in the midline posteriorly, and in an altered position of the acetabula, with dislocation of the hips making walking difficult or impossible.

Other congenital abnormalities of the spine and ribs are often associated with congenital deficiencies of the lower vertebral segments and include spina bifida, hemivertebrae, and meningocele. Coexisting soft tissue anomalies include: arthrogryposis, anal defects, cleft lip or palate, hernia, genitourinary deficiencies and malformations, partial agenesis of extremities, congenital heart disease, and reduplications of colon, bladder, and penis.

Fig. 3. Anteroposterior roentgenogram of the pelvis at the age of six months. The sacrum and coccyx are absent, but the pelvis is normal in contour.

Fig. 4. Anteroposterior roentgenogram of the pelvis at the age of five and one half years. The bony pelvis is narrowed, elongated, and slightly asymmetric; these are weight bearing effects.

A deficiency of a primary organizer is believed to be the basis for agenesis of the lower vertebral segments. The abnormality develops early during embryonic life, since ossification of the first sacral segment begins during the eight or ninth week of fetal

life. Most cases show a complete absence of vertebral development below a certain level, and sometimes malformation of those lower segments which are present, suggesting that the inhibitory factor proceeds in a caudal to cephalad direction.

In animals, deficiencies in the caudal vertebrae have been induced by subjecting the embryo to the influence of high temperatures, lithium salts, insulin, ultraviolet rays, or vitamin A deficiencies. In the human, possible contributing maternal factors are poor nutrition, certain illnesses, fever, diabetes mellitus, and the presence of toxic substances in the circulation. Some cases may be due entirely to heredity.

SUMMARY

A case of congenital absence of the sacrum and coccyx is described. Deficiencies in the lower spinal nerves and muscular maldevelopment of the lower extremities are associated with this abnormality. Clinical features of this unusual congenital anomaly are reviewed.

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The author wishes to express his appreciation to Dr. Lynn A. Ferguson.

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DEFECT OF THE CORPUS CALLOSUM AND CONGENITAL OCCLUSION OF FOURTH VENTRICLE WITH TUBEROUS SCLEROSIS*

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DURING the last decade it has been realized that many fetal abnormalities, thought to be hereditary in origin, may be results of fetal disease during intrauterine life and not inevitable. The protection of the fetus by the placenta is now known to have been greatly over-rated and most viruses, bacteria and many common chemicals can pass through the villi into the fetal circulation. Primitive cells in the differentiating fetus are particularly susceptible to permanent injury by viruses and chemicals which may have no noticeable clinical effect on the mother after transfer to her unborn child.[13]

When fetal organogenesis is experimentally interfered with, the end results are often common to varied initiating agents, and depend more upon the critical timing of the injury. Clearly, the probable agents are most difficult to trace many months later at birth. Willis stated that "while scattered observations . . . are of doubtful significance and statistically valueless, it is important that they should be recorded, for some of them may provide clues worth following in further inquiries into the histories of malformation-producing pregnancies and in further experimental work." With this purpose in mind the authors wish to document this single case of agenesis of the corpus callosum associated with tuberous sclerosis and other abnormalities of the brain.

REPORT OF A CASE

Baby W., a newborn male, was seen because of a large head and a history of two "blue spells" twelve hours following birth.

Physical examination showed that the head was large, especially in the occipital region; bilateral cephalohematomata were also present, the larger on the right side. The anterior fontanelle was widely patent, the posterior small. The child was lethargic, listless and quite hypotonic. The fundi were normal, there were no abnormal neurologic signs, and the neck was not stiff. Bilateral subdural punctures through the anterior fontanelle revealed no evidence of subdural hematoma. A ventricular puncture was carried out and 10 cc. of air substituted for ventricular fluid on the left side. The ventriculograms were interpreted as indicating an agenesis of the corpus callosum, with the possibility of a concomitant tuberous sclerosis because of the irregularities of the walls of the ventricular cavities (Fig. 1–4).

The child died six weeks later, after many more "blue spells" from staphylococcal bronchopneumonia.

At autopsy the main abnormalities were found in the brain (Fig. 5–9). On microscopic examination of the nodular areas, Luxol fast blue and other stains showed a loss of normal cortical lamination and myelin meshwork with marked glial proliferation including scattered occasional large protoplasmic astrocytes. These changes were not restricted to the visible nodular areas, but were present to some degree throughout the cerebrum, as is common in tuberous sclerosis. None of these lesions were found in the brain stem or cerebellum. The fourth ventricle formed a cyst, lined by smooth ependyma and showed no foramina. The aqueduct was dilated, unkinked and reached 3 mm. in diameter.

A 2 mm. tubular hamartoma was found at the corticomedullary junction of one pyramid in the left kidney. No other abnormalities were detected.

DISCUSSION

It was formerly believed that the protec-

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Fig. 1. Ventriculogram, anteroposterior view. The space between the anterior horns is occupied by cerebral tissue anterior to the plane of the septum pellucidum. The lateral walls of the anterior horns are irregular due to nodules of gliosis, while the roofs are deformed by masses of tuberous tissue. The arrow indicates an abnormally peaked dorsal margin of the lateral ventricle (see also Fig. 5).

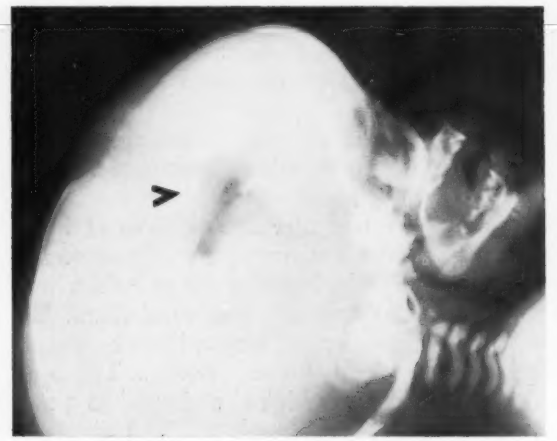

Fig. 2. Ventriculogram, brow up lateral view. Three features are demonstrated: (1) Relatively small size of the anterior horns of the lateral ventricles; (2) marked widening of the foramen of Monro due to absence of the fornix which normally forms its anterior margin. The anterior wall of the third ventricle and the anterior horn of the lateral ventricle show a continuous line; (3) a central radiolucent shadow demonstrates the absence of the septum pellucidum and free communication between the lateral ventricles (arrow).

tive barrier of the placenta was so complete that congenital anomalies were probably hereditary and unavoidable. However, proof of genetic origin in many of the most common defects, especially cardiac, has not been forthcoming in the literature. Even occurrence in twins or siblings, so often assumed to be prime evidence of hereditary origin, may equally be the result of common exposure to environmental causes which go unrecognized.[13]

Experimentally it would appear that defects and malformation correspond more

Fig. 3. Ventriculogram, posteroanterior view. Widely separated and enlarged posterior horns of the lateral ventricles are seen with medial and cephalad extension of the roofs in a bicornuate deformity. Irregular nodules are seen in the walls of the lateral ventricles particularly on the right side due to tuberous gliosis corresponding with "candle guttering" seen in the gross specimen (arrow). The bilocular midline collection of air interposed between the lateral ventricles represents the posterior extent of the abnormal cavity joining the two lateral ventricles, which is ordinarily occupied by the septum pellucidum. The "partition" is unexplained.

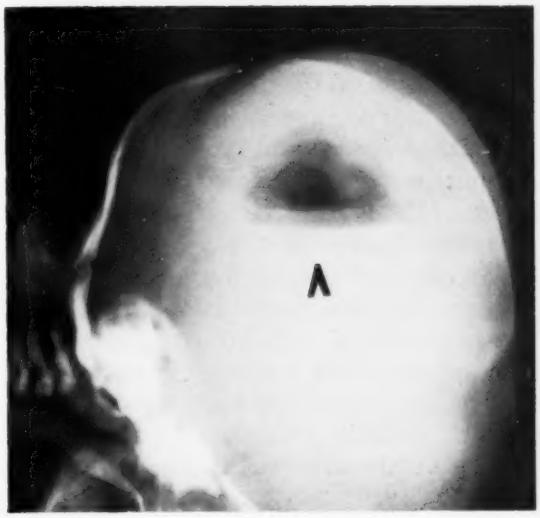

Fig. 4. Ventriculogram, brow down lateral view. Both occipital regions of the lateral ventricles are grossly dilated, compared with the small underdeveloped anterior horns. The sharply circumscribed radiolucent shadow (arrow) represents the abnormal common cavity between the two lateral ventricles occupying the position of the absent septum pellucidum.

Fig. 5. Coronal section of the brain through the atria of the lateral ventricles, thalami and floor of the fourth ventricle (from behind). The lateral ventricles present as a common cavity with complete absence of a septum pellucidum and corpus callosum. Medially rotated gyri and sulci of the sagittal fissure form the medial part of the roof of a common ventricular cavity. The sulcus to the left of the midsagittal plane superiorly (upper arrow) represents the peaked dorsal margin of the lateral ventricle (compare with Fig. 1). A mass of tuberous gliosis deforms the roof of the atrium on the left (lower arrow). The temporal horns are relatively normal, but no hippocampal stripes or olfactory nerves can be detected.

with the time at which a harmful agent damages embryonic processes which are actively proliferating. As the various organs forming at the same time are subject to the same noxious agents, it is thought that this may be a reason why multiple anomalies tend to appear rather than solitary ones. No evidence has been recorded to show that agenesis of the corpus callosum has any hereditary basis in humans. It is stated to be a familial occurrence in the mouse.[7] A considerable variety of anomalies has been reported in association with it, including cerebral microgyria, cerebellar hypoplasia, stenosis of the aqueduct, porencephaly, patent ductus arteriosus, bifid ribs and multiple dental cysts. None of these appear

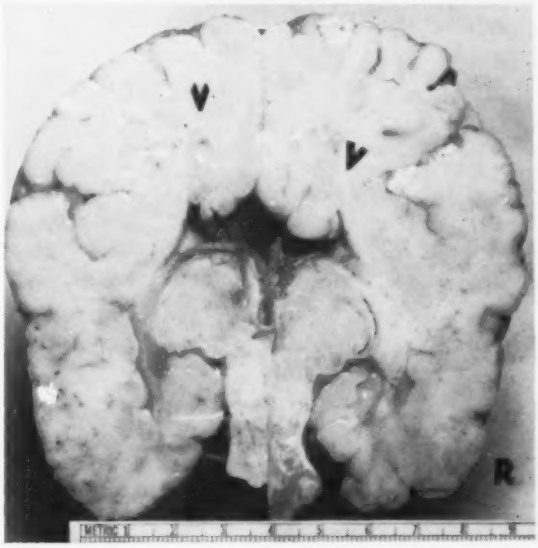

Fig. 6. Coronal section of brain anterior to that in Figure 5 seen from behind. The common cavity of the lateral ventricle is seen with medially rotated gyri in the roof. Bicornuate deformity of the roofs of the lateral ventricles is just appearing (arrows). Glial tissue, replacing normal cortex, obliterates the lateral cortical sulci and enlarges the hemispheres, especially the temporal lobes.

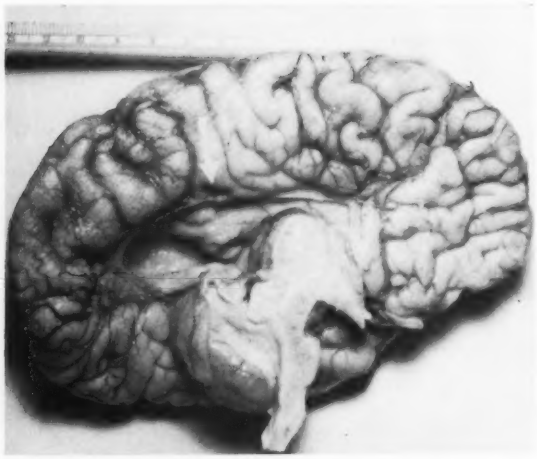

Fig. 7. Medial aspect of the left cerebral hemisphere showing absence of corpus callosum and rhinencephalon, cystic fourth ventricle with rudimentary vermis and hypoplastic pons. Note the pseudocortical paraventricular nodules of tuberous sclerosis ("candle gutterings"). Micro- and macrogyri make up the cortical surface of the hemisphere. No cingulate gyrus can be detected.

with undue frequency. However, it regularly concurs with failure of development of the rhinencephalon which includes the septum pellucidum, fornix, fimbria, hippocampal gyri and olfactory nerves. Both the corpus callosum and rhinencephalon begin as thickenings of the lamina terminalis at about the same time in embryonic life and grow posteriorly in ram's horn fashion together with the evolution of the temporal lobes. Because agenesis affecting both formations appears to be the rule, it is clear that absence of the corpus callosum cannot be a reversion to a more primitive form of brain, for the rhinencephalon is phylogenetically older.

No maternal disease was detected at any stage in our case. No cause for the condition is known, but it has been suggested as a possible sequel of maternal rubella during pregnancy in one report.[4] We could find records of only 2 instances of somewhat similar combinations of callosal defect and tuberous sclerosis in the litersture.[2,3]

The absence of a roof to the third ventricle or the presence of a common ventricular connection causes the most characteristic roentgenographic appearance.[5] The lack of formation of the genu of the corpus callosum is responsible for the failure of forward extension of the lateral ventricles beyond the plane of the foramen of Monro. On the other hand, the dorsal margins of the lateral ventricles are peaked and the posterior horns are dilated due to the absence of periventricular matrix and tapetum, which are normally in active forma-

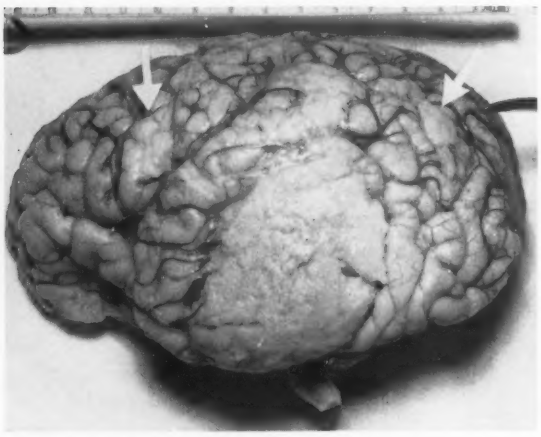

Fig. 8. Lateral view of the left cerebral hemisphere. A plaque of white mammillated tuberous tissue replaces the cortex of the parietal and temporal lobes. Isolated islands of similar nature can be seen (arrows).

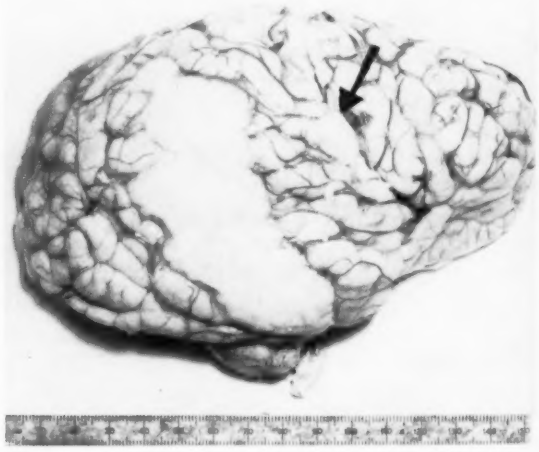

Fig. 9. Lateral view of the right cerebral hemisphere. The main plaque of tuberous tissue almost forms a mirror image of that on the left side. One apparently isolated island of similar tissue is marked (arrow).

tion at the same time as the corpus callosum.[6]

Tuberous sclerosis is known to have a strong genetic basis, but is rarely observed in the newborn. This suggests that in some way the rate of development was enhanced in this case.

Lipoma of the corpus callosum often occurs with incomplete formation of the corpus callosum. These masses seem to be hamartomatous, arising in tissues around the anterior cerebral arteries, moulding supracallosal structures, including the falx and preventing their further evolution by obstructing their growth rather than a basic developmental defect of the corpus callosum itself.[8,10]

In contradistinction to the above, our case is an example of an arrest of development of the corpus callosum and rhinencephalon occurring before the end of the third month of fetal life.[1] The foramina of Magendie and von Luschka begin to appear about the fifth to sixth week of embryonic life.[12] In our case their absence led to the development of a grossly dilated fourth ventricle.[11] There is, therefore, good reason to believe that all the lesions in our case dated from about this time.

In retrospect the selective occipital enlargement of the head noted clinically was due to the dilatation of the fourth ventricle. This feature has been noted previously by Matson.[9]

SUMMARY

A case of a complete defect of the corpus callosum and rhinencephalon, with atresia of the foramina of Luschka and Magendie and tuberous sclerosis is described. These lesions probably date from about the sixth week of embryonic life. They are reported to draw attention to the earlier phases of malformation-producing pregnancies.

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PNEUMOCYSTIS CARINII PNEUMONIA*

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THE first cases of pneumocystis Carinii pneumonia were reported in this country by Lunseth *et al.*[26] in 1955. Since that time many cases have been recorded from all over the United States and Canada. Most of these reports include only a few cases observed by the authors. No one in this hemisphere has, as yet, seen as large an outbreak of this disease as that reported by Bachmann[5–7] in Cologne and by Freudenberg and Tobler[18] in Switzerland. It would seem, therefore, that this disease, in this country, is still somewhat unusual or exists unrecognized.

We observed a few cases of pneumocystis Carinii pneumonia and were intrigued by the roentgen appearance of the chest in these children. We then studied the roentgenograms of the children involved in the epidemic in Cologne, Germany and it seemed that the roentgen findings, although not pathognomonic, were so similar in all cases that they could be called characteristic for this disease. After we had studied the roentgenograms of over 100 cases and had a better understanding of the roentgen appearance of this entity, we found 3 cases presenting this lesion handled by one pediatrician in our city. It seemed to us, therefore, that the disease is not as rare in this country as it may appear from the literature, but that it goes undiagnosed in too many cases. The purpose of this paper is to alert the radiologist who has the opportunity of seeing these cases to the signs which aid in their recognition and diagnosis.

ETIOLOGY

The disease is caused by a protozoon,[19,22,23,43] the pneumocystis Carinii, first described by Chagas[14] in 1909 and then by Carini,[13] whose name was given to the organism. The early investigators saw this organism only in animals. The first case of pneumocystis Carinii seen in a human was described by Van der Meer and Brug[36] in 1942 without them identifying it. Otto Jirovec demonstrated the organism in the lungs of 16 children (observed by Vanek and Jirovec[37] between 1945 and 1951) who died of an interstitial type of pneumonia. The clinicopathologic picture of the disease was described in 1913 by Wätjen[40] and in 1927 by Feyrter[17] and others.[28,32,35] This unusual interstitial pneumonia in early infancy was the concern of many clinicians and pathologists.[4,10,31] Using Koch's postulates, it has not been definitely proved that the pneumocystis Carinii protozoon has produced this particular type of interstitial pneumonia. However, in all cases of this disease the organism has been found. It is, therefore, assumed that this otherwise harmless saprophyte is a causative factor in susceptible patients.

The reason for an epidemic outbreak of this disease and/or its sporadic occurrence is not yet clear. It could well be that adults, who are otherwise free of clinical symptoms and show no roentgenographic findings, are the carriers of the disease. The complement fixation tests recently developed[9,39] may shed further light on this problem. Ewerbeck[16] demonstrated clinically that the adult is a carrier of the protozoon and strict isolation and sterilization methods may well prevent spread of the disease.

CLINICAL FEATURES

Pneumocystis Carinii pneumonia usually occurs in children between the ages of two and five months, and most com-

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monly in premature, underweight children, or in children whose resistance is decreased. This type of interstitial pneumonia has also been described in some adults but in all these cases a marked debilitating disease was present.[38] The incubation period is approximately forty to fifty days.[6,24] The lethality of the disease lies between 30–50 per cent.[7,8,25,40] This high death rate forces us to be concerned.

The clinical picture may be very stormy. An apparently well child may in a few hours develop severe dyspnea, tachypnea, cyanosis and facial paleness ending in sudden death in a few hours or in from two to five days. Pathologic examination has shown this to be the cause of death in some infants who were apparently well when they were put to bed in the evening and were found dead in their cribs on the following morning.[8] On the other hand, the disease may run a relatively insidious course in the beginning without alarming either the child's parents or his doctor, and then suddenly attack the patient with full severity. Also, the symptoms may increase slowly until the full clinical picture is present. The infant is completely apathic, in a collapsed condition, with a frightful face, a tachypnea between 80–120 and severe dyspneic cyanosis, using all his auxiliary respiratory muscles to the fullest extent the prostrate condition allows.[1,5,6,7,8,21,26,33]

In contrast to this alarming clinical picture are the physical findings and laboratory studies. The lungs on auscultation and percussion do not appear unusual; one may hear only a fine, paper-like crackle over the lower lung fields. Electrocardiographic studies do not reveal a myocardial insufficiency and are normal. The blood study may show elevation of the white blood cell count but is otherwise undiagnostic.

Premature infants in the sixth to eighth week of life with plasma cell pneumonia demonstrate a drop in the gamma globulin fraction and an increase in the alpha globulin fraction. If the child contracts this disease between the tenth and thirteenth weeks of life, an increase in the alpha and gamma fractions with a depression of the albumin fraction is noted.[12,20,30] Occasionally, elevation of the plasma calcium levels is seen.[12] In most cases, the pneumocystis Carinii can be found in the sputum. A special staining method has to be used with a phase microscope.[5,34] The absence or nondemonstration of the protozoon in the sputum does not exclude the diagnosis of pneumocystis pneumonia.

ROENTGEN FINDINGS

The clinician, therefore, has to depend to a great extent on the roentgenographic studies, in addition to his clinical observation, in making a diagnosis. The chest roentgenograms are usually characteristic[21] and present the most valuable contribution to the clinical diagnosis. It is surprising that the roentgenologic interpretation is treated so lightly; only a few articles place adequate importance on the value of these findings.[28,41] Unfortunately, the differential diagnosis of an interstitial type of pneumonia includes some thirty different types of disease.[43] The majority of them can be differentiated by the roentgenographic study alone, but in many instances the combination of the roentgen findings, age group, specific history or evident clinical findings must be taken into consideration.

The changes on the chest roentgenograms seen most commonly (Fig. 1) are those of an extensive bilateral bronchopneumonia with generalized, localized and interstitial emphysema, often with small atelectatic segments. In 150 chest roentgenograms reviewed for pneumocystis Carinii pneumonia, the ground glass appearance described in many publications was not observed by us. The changes seen in these lungs seem to spread from the hilar areas into the periphery. No signs of hilar lymphadenopathy were seen. Fine lines of increased density fanning out from the hili into the periphery are observed leaving an emphysematous peripheral border of the lungs free of involvement (Fig. 2). These linear densities are surrounded by more or

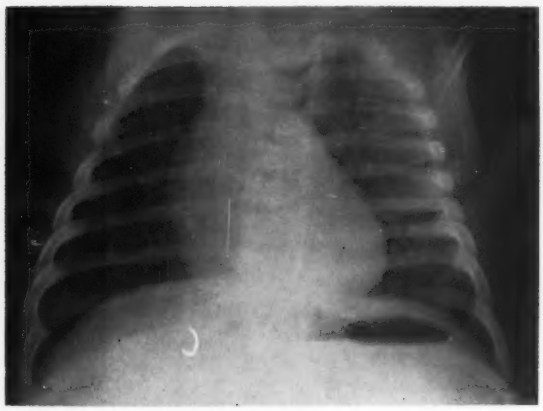

FIG. 1. Chest roentgenogram of a three month old male four days after hospital admission. Diagnosis of pneumocystis Carinii was established at autopsy four days after this roentgenogram was taken.

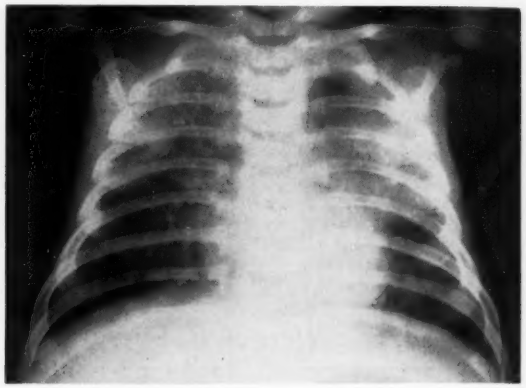

FIG. 3. Chest roentgenogram of a three month old female taken one week after admission and ten days after the onset of clinical symptoms. Diagnosis of pneumocystis Carinii was confirmed at autopsy fourteen days after the onset of symptoms.

less fine to coarse, patchy densities. Sometimes these patchy densities conglomerate to form pneumonic infiltrates affecting larger lung segments (Fig. 3). Both lungs were always involved, the upper lobes most frequently, and often all five lobes showed marked changes which were most obvious in the left upper lobe. The lower lobes were less markedly infiltrated but demonstrated definite emphysematous changes. We observed the emphysematous involvement best in the lateral views. The heart, aorta and pulmonary vessels showed no evident changes and we did not note any pleural reactions.

The extent of pulmonary involvement could not be used as a prognostic sign (Fig. 4 and 5). The early stages of the disease have not definitely been demonstrated on roentgenograms because the patient is usually not ill enough to warrant an early roentgen study. Obviously, no roentgenograms are available of children

FIG. 2. Chest roentgenogram of a two and one-half month old female ill for two days. The patient died one day later of pneumocystis Carinii diagnosed at autopsy.

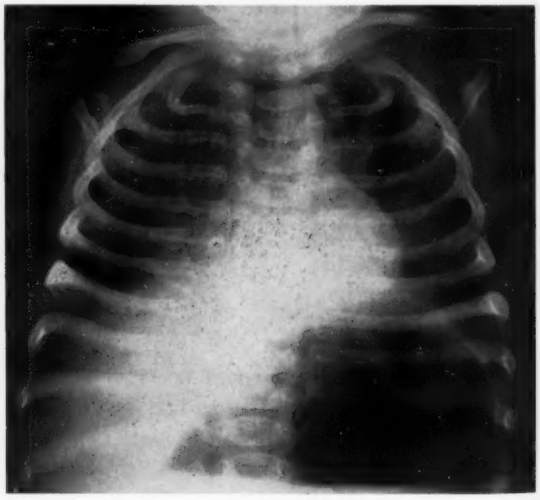

FIG. 4. Chest roentgenogram of a fourteen week old female child taken on admission to the hospital after one day of clinical symptoms. The patient died the same night and a diagnosis of pneumocystis Carinii was confirmed at autopsy.

Fig. 5. Chest roentgenogram of a fourteen week old male taken on admission to the hospital after one day of clinical symptoms. The patient survived and was discharged from the hospital after three months.

who died suddenly from this disease. There appears to be little doubt that the chest roentgenograms of the children whose sudden death is attributed to the disease would not have differed from the chest roentgenograms of the children whose deaths occurred in the later course of the disease. This conclusion is reached because of the parallel findings in the lungs in all these cases at necropsy.

The clinical course of the disease lasts about six to eight weeks but roentgenographic changes are present for a much longer period of time. This definitely poses a difficult differential diagnostic problem. Unfortunately, not enough follow-up studies are available. In the cases we have seen, the lungs did not appear normal two years after the children had recovered symptomatically (Fig. 6, *A–D;* and 7, *A* and *B*).

The roentgen findings in the acute stage of the disease must be differentiated from extensive bronchopneumonia of a bacterial, viral or tuberculous origin. Aspiration pneumonia, giant cell pneumonia and cytomegalic disease occurring as an interstitial pneumonia, measles and pertussis pneumonia can easily be considered as being consistent with gamma globulin abnormalities.

PATHOLOGY

The pathologic changes of the disease have been extensively discussed since its recognition.[12,15,29,38] It is rarely mentioned that the organism can spread through the blood and lymph vessels and may be found in the kidneys, brain and liver, in addition to its typical appearance in the alveoli of the lung.

TREATMENT

At the present time no specific therapy is known. All antibiotics, chemotherapeutic agents, antihistamines, cortisone, and antimalaria agents have failed. Symptomatic therapy with oxygen and careful nursing are the only measures that afford relief and make the patient more comfortable. The use of antibiotics is recommended to control infection from secondary invaders.

DISCUSSION

Interstitial plasma cell pneumonia due to pneumocystis Carinii is a highly contagious disease for the susceptible individual, usually the infant between two and five months of age, premature, underweight, or debilitated for some other reason. The high (30–50 per cent) mortality rate should point up the importance of further study of this entity.

We do not believe that the disease is as rare as is indicated in the literature but that it is too often undiagnosed. In many cases it may run such a moderate course that it may be clinically unnoticeable and only the incidental chest roentgenographic examination may point to the diagnosis. This has already been reported by Sternberg and Rosenthal[33] and we made similar observations in two sets of twins. One twin showed clinical evidence of the disease and had to be hospitalized but the other was symptom free. The first knowledge of involvement of the lungs was by chest roentgenograms made routinely on admission (Fig. 8 and 9).

The recognition of these cases is very important as the clinically silent case can very well be the cause of epidemics previously described in hospitals and children's homes. We believe that one would

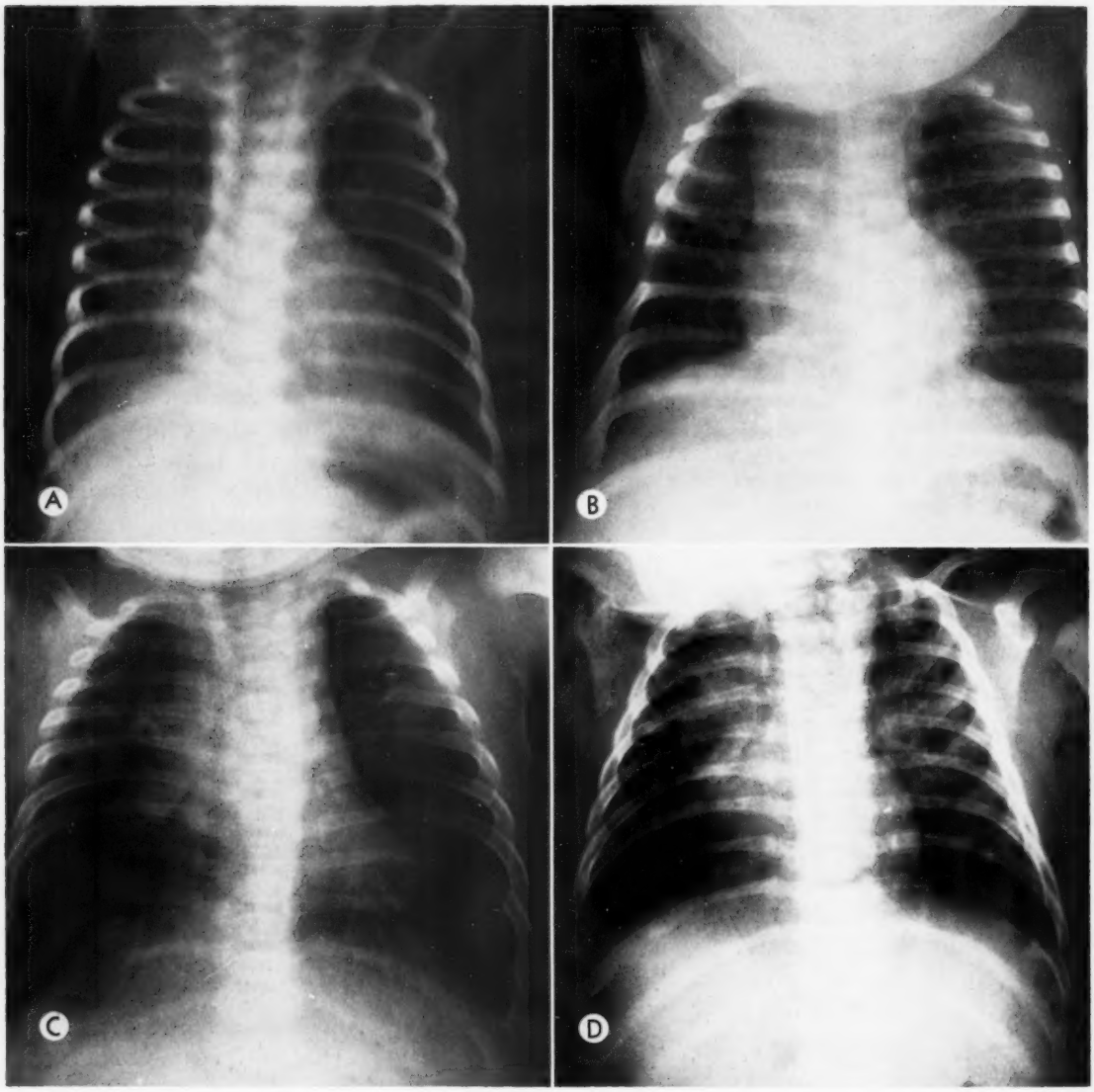

FIG. 6. (*A*) Chest roentgenogram of a ten week old female, ill for two weeks, taken at the most acute stage of the clinical symptoms. (*B*) Chest roentgenogram taken six weeks after *A* at the time of discharge from the hospital when the patient was clinically symptom free. (*C*) Roentgenogram taken four months after the clinical onset of the disease. At this time the child had been symptom free for three months. (*D*) Roentgenogram taken five months after *B*. There were no clinical symptoms and the child was perfectly well.

not be wrong, in view of the high mortality of this disease, to make a diagnosis of pneumocystis Carinii pneumonia in infants between the ages of two and five months who are underweight, debilitated or prematurely born; who show signs of increasing dyspnea and cyanosis with little cough or temperature elevation and without significant physical findings or characteristic laboratory studies; and whose chest roentgenograms demonstrate pronounced emphysema and findings consistent with diffuse bilateral bronchopneumonia. Such a diagnosis would result in the immediate use of sterile procedures and strict isolation of the patient. To date, this is the only successful measure for controlling the disease.

The chest roentgen findings alone are not diagnostic of pneumocystis Carinii pneumonia but they are consistently similar in all cases and are, therefore, characteristic. The extensive bilateral involvement of the

lungs and the concomitant generalized interstitial emphysema are rarely seen in any other type of interstitial pneumonia in this age group.

SUMMARY

Interstitial plasma cell pneumonia due to the pneumocystis Carinii protozoon is a disease of early childhood which is not as rare as was previously believed. Awareness of the disease may lead to the diagnosis of many more cases and may prevent unnecessary infantile deaths. The diagnosis can be made by the characteristic roentgen findings in the chest correlated with the clinical history and physical findings.

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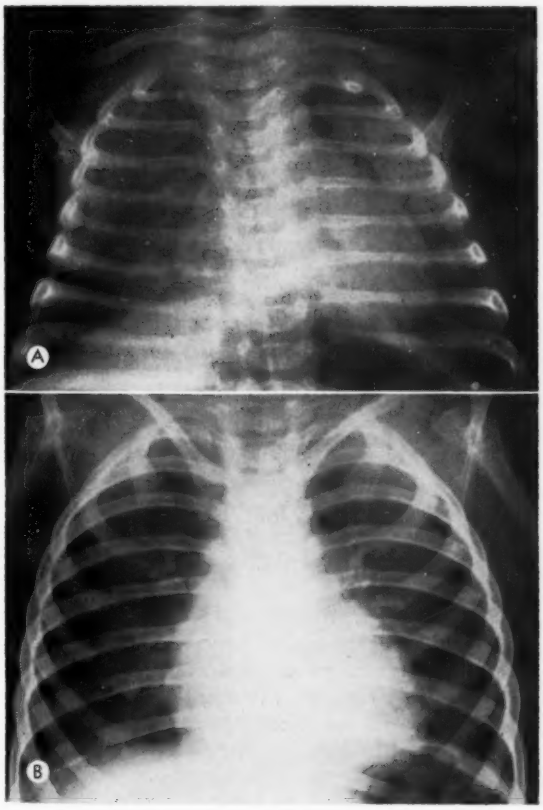

Fig. 7. (*A*) Chest roentgenogram of a three month old male taken at the height of the disease, two weeks after the onset of clinical symptoms. (*B*) Same patient as in *A* after he had been symptom free for two years.

Fig. 8. Chest roentgenogram of a three month old male at the time of hospital admission with severe clinical symptoms. The patient survived.

We wish to express our thanks to Leonard Montag, M.D. for allowing us to use information from his private files for the demonstration of his cases in our Figures 8 and 9.

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Fig. 9. Chest roentgenogram of the twin brother of the patient in Figure 8. This child was clinically well. Roentgenograms were taken because of his exposure to the disease. The patient never was hospitalized and never presented clinical symptoms.

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ROENTGEN SIGNS OF PNEUMOPERITONEUM IN THE NEWBORN*

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A DELAYED diagnosis of pneumoperitoneum in the newborn infant is commonly associated with fatal consequences. Perforation can occur anywhere along the gastrointestinal tract of infants, frequently producing pneumoperitoneum. The causes of perforation are many and have been described elsewhere.[2,9] The clinical features and the treatment of this condition have been recently described by Hamrick.[5]

A careful study of the roentgenograms of these patients discloses the presence of free air in the abdomen, by which an early diagnosis can be established, thus reducing the high mortality rate.

ROENTGEN DIAGNOSIS

The supine roentgenogram. When perforation of the gastrointestinal tract occurs into the peritoneal cavity, rapid accumulation of air ensues, producing abdominal distention. Unless the possiblity of pneumoperitoneum is suspected, the roentgen examination of the abdomen in these infants is frequently made in the supine position. The diagnosis of free air in the peritoneal cavity can then be established by the presence of a central collection of air beneath the anterior abdominal wall, which adopts the round or oval shaped contour of the child's abdomen (Fig. 1).

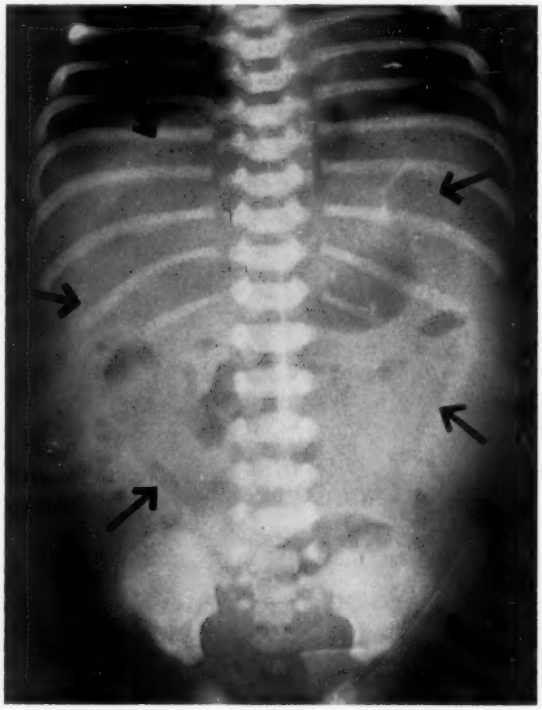

Fig. 1. Supine roentgenogram of the abdomen of a newborn infant with gastric perforation. An oval shaped collection of air is seen occupying the central portion of the abdomen (arrows).

The detection of this roentgen sign can be made shortly after the onset of symptoms. When the pneumoperitoneum is severe, the air bubble tends to bulge the abdominal wall, outlining structures located anteriorly. The urachus and/or the falciform ligament can then be seen as a thin dense line parallel to the midline and dividing the gas bubble in two segments (Fig. 2). The size of the air bubble is variable, depending on the amount of air swallowed by the infant, the time lapse after the onset of perforation and its location. If the amount of free peritoneal air is small, the gas bubble may go undetected as it may be assumed to be part of the gaseous pattern of the intestinal tract.

The erect roentgenogram. When perforation of a hollow abdominal viscus is suspected, the roentgen examination of the abdomen performed with the infant in the erect position is regarded as ideal.[8] Even a small amount of intraperitoneal air will visualize as a radiolucent line underneath

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the diaphragm in this roentgenogram. Air in large amounts tends to surround the liver and to separate it from the right hemidiaphragm. The distance between the stomach fundus and left hemidiaphragm is also increased and all the upper abdominal structures are displaced downward and centrally; the degree of separation of the diaphragm from these structures is related to the degree of pneumoperitoneum (Fig. 3).

Air-containing loops of bowel are visualized as somewhat deflated when the pneumoperitoneum reaches large proportions. The presence of free fluid is detected in the erect roentgenograms as infraperitoneal fluid levels.

MacGillivray and co-workers report on the use of roentgenograms made in the inverted position in these cases.[6] These roentgenograms show the presence of a large amount of air separating the abdominal contents below from the abdominopelvic boundaries above. Gas in the scro-

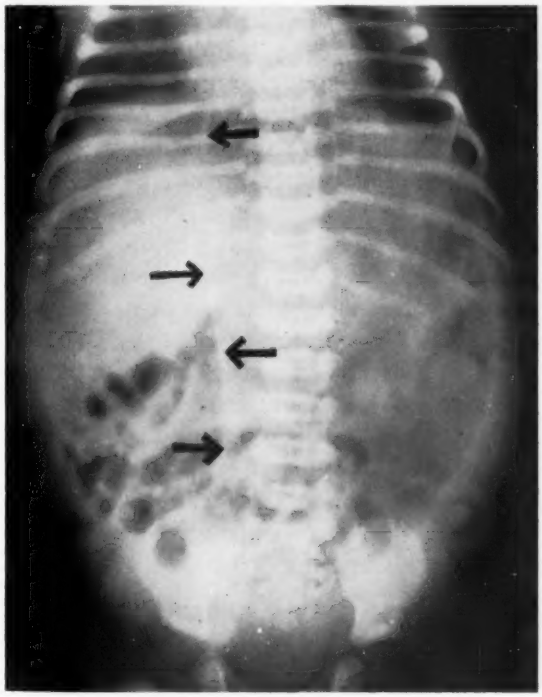

Fig. 2. Supine roentgenogram of the abdomen in a five day old infant with marked abdominal distention. Note the extensive amount of free air in the abdominal cavity outlining and bulging its lateral walls. The thin line seen parallel and to the right of the spine represents the projection of the falciform ligament (arrows).

Fig. 3. Same patient as shown in Figure 2. Erect roentgenogram shows a large amount of free air under the diaphragm.

Fig. 4. Lateral recumbent roentgenogram demonstrating a large air-fluid level extending from the diaphragm to pelvis. This is characteristic of pneumoperitoneum with peritoneal fluid.

Fig. 5. Line drawing showing the anterior semilunar collection of air separating the viscera from the abdominal wall in a case of pneumoperitoneum. This sign is observed on lateral roentgenograms.

tum and subcutaneous tissue of the lower abdominal wall is also seen.

The lateral roentgenogram. The presence of pneumoperitoneum in the newborn can also be detected in the lateral recumbent position with roentgenograms taken with a horizontal beam. This view is used routinely in some institutions in cases of abdominal distention in the adult. The lateral roentgenogram shows the free air separating the intra-abdominal structures from the abdominal wall (Fig. 4).

Another interesting roentgen sign on lateral roentgenograms consists of a semilunar translucency located anteriorly to the abdominal viscera and separating them from the anterior abdominal wall. This represents free air in the peritoneal cavity (Fig. 5).

COMMENT

Perforation of the gastrointestinal tract in the newborn infant is uncommon but, when present, occurs most frequently in the stomach and duodenum. Stomach perforation produces pneumoperitoneum readily but small bowel perforation is seldom associated with free abdominal air. The earliest roentgenographic sign of pneumoperitoneum is that of air underneath the diaphragm which can be detected only when roentgenograms are taken in the erect position. In other positions, the diagnosis of pneumoperitoneum can sometimes be missed due to a lack of familiarity with the roentgen signs. Although upright films are preferable to those taken in the supine positions, frequently the presence of intestinal perforation is not suspected and roentgenograms are taken with the infant on his back.

Braunstein[3] was the first to describe the visualization of the outline of the falciform ligament of the liver against the radiolucency of free abdominal air in the supine position. Astley[1] describes in his book the presence of a central abdominal translucency in this position, corresponding to a bubble of free air under the abdominal wall. Miller[7] regards this finding as pathognomonic and calls it the "air dome" or "football" sign. Although this may be mistaken for intestinal dilatation due to obstruction or volvulus on the supine roentgenogram, a positive diagnosis of pneumoperitoneum can be established on erect roentgenograms. It is also possible to obtain the same results when the inverted position is used, holding the infant by its feet; thus air will tend to fill the pelvic cavity.[6]

On lateral roentgenograms, the semilunar collection of air anterior to the abdominal viscera has been observed by Pendergrass and Booth,[8] and Fomon and co-workers.[4] This is also characteristic of free air in the peritoneal cavity and a helpful sign when these roentgenograms are studied.

SUMMARY

The roentgen signs of pneumoperitoneum in the newborn are briefly reviewed. Emphasis is placed on the less commonly recognized findings seen on roentgenograms taken in the supine and lateral positions. Familiarity with these signs assists

the radiologist in establishing an early diagnosis, thus decreasing the high mortality rate associated with this condition.

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IMPERFORATE ANUS FROM A ROENTGENOLOGIC VIEWPOINT*

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CONGENITAL anorectal malformations have an incidence of one in 5,000 births, making "imperforate anus" one of the most common major congenital anomalies. The radiologic literature on this subject is rather meager, but comments on the radiologic aspect are found in the surgical literature.[7,10,13] Such terms as "helpful," "misleading,"[4] "ingenious," and "confusing"[5] have been used to describe the role of roentgen studies in this field.

To evaluate the radiologic problems and results, we have reviewed the literature and collected 31 cases that have been seen in the Miami area.

EMBRYOLOGY

It is not our purpose to discuss extensively the embryology of anorectal malformations, as there are many excellent papers on this subject.[1,2,7] A brief summary is pertinent, however, as failures in the normal development give rise to the malformations encountered clinically, and some knowledge of the embryology is helpful in understanding them.

If the division of the cloaca by the urorectal septum into a urogenital sinus anteriorly and a rectum posteriorly is not complete, a "fistula" between the rectum and bladder, urethra or vagina persists. The embryologic error can be explained by the above mechanism, whether it represents true fistula formation or failure of anal migration.

The cloacal membrane is divided into an anterior urogenital membrane and a posterior anal membrane by the downgrowth of the urorectal septum. By the eighth week of embryonic life the anal membrane, which separates the rectum from the exterior, is ruptured normally by ingrowth of the ectodermal anal anlage (proctodeum). Thus the anus and rectum become one continuous canal.

The time of the developmental arrest appears to account for the various malformations. Usually there is a failure of both of the developmental steps outlined above. Practically all infants with imperforate anus have a connection between the rectum and either the urinary tract, perineum, or vagina.

TYPES OF FISTULAS

The most common type of "fistula" in the male is the rectourethral; rectoperineal and rectovesical fistulas may also occur. In females, however, fistulas to the urinary tract are extremely rare, and the most commonly encountered connections are with the vagina (high or low), the introitus, and the perineum. A few cases of multiple fistulas have been recorded.

CLASSIFICATION AND THE ROENTGENOLOGIC PROBLEM

Although there are numerous classifications of the congenital anorectal anomalies, the time-honored one by Ladd and Gross[7] (Table I) has gained most wide acceptance in the United States. Recently, Scott and Swenson[11] outlined a classification incorporating some of the concepts of Browne,[3] which we believe has helped to clarify the diagnostic and treatment problems. These authors eliminate Type II of Ladd and Gross and separate Type III into high and low level varieties. Browne feels that the Type II lesion of Ladd and Gross may not exist, and that cases assigned to this group may be either the "microscopic

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anus" (variant of Type I) or a covered anus (Type III variant) which is unrecognized. Type IV lesions are evidently rare. Of the four classes discussed by Ladd and Gross, Type III is by far the most frequent and the one that chiefly concerns the radiologist.

The concept of two major groups of deformities—those with rectal agenesis and those without, but with an anus that is malformed or misplaced—was introduced by Browne,[3] whose classification is included in Table I. His viewpoint, which has gained acceptance in England, is that the essential difference between the two groups of lesions is that the first has a bowel terminating above the levator ani, whereas the second has a bowel which passes through this important part of the sphincter mechanism. The stenosed, covered, and ectopic anus lesions are anatomically low malformations.

Kjellberg, Ericsson, and Rudhe[6] state that in their series two types can be distinguished. In the first (rectal atresia), the lumen is constricted or obliterated at the level of the second sacral segment and the vesical trigone. In the second (anal atresia), the occlusion is just proximal to the proctodeum. They have "not observed rectal or anal atresia at any intermediate site," nor have they "found any definite support for this possibility in the literature."

That these abnormalities are either high or low has been expressed also by Stephens.[12] He located the most proximal constriction at the pubococcygeal line, whereas Scott and Swenson used this line as the division between high and low types of malformation. They state that the line should be drawn between the lower border of the pubis and the sacrococcygeal junction, and that this line indicates the position of the pelvic floor.

Ladd and Gross consider lesions 1.5 cm. or more above the anal dimple as high and unsuitable for repair from below. It is readily apparent that this matter is of some importance when one considers the fact that the surgical results are greatly influenced by the proper choice of operation. According to the various criteria outlined, if the dividing line is placed too high, surgery from below might be improperly attempted; if the line is placed too low, a more difficult operation with a rather high percentage of morbidity might unnecessarily result.

Potts and co-workers[9] have stated: "Somehow or other the upside-down roentgenograms of an infant with atresia of the rectum, as suggested by Wangensteen and Rice,[13] have impressed medical students." Other authors[4,5,11] decry the inaccuracy of roentgenologic methods and admit having been led astray by the inverted technique. Some authors have pointed out pitfalls to be considered.[4,6,7] These seem to be:

1. The method is reliable in low lesions only if the sphincters present are relaxed.
2. Meconium may be filling the distal portion of the blind segment so that the end of the gas column is not at the end of the bowel.
3. The gas may not have had sufficient time to outline the lowest portion of the bowel if the roentgenograms are made too soon after birth. Making the roentgenograms twelve to twenty-four hours after birth will usually overcome this objection.
4. The type of marker and its placement may be improper.
5. The roentgenographic enlargement and distortion may be significant.

These objections could be negated partially or completely by modifications of technique. However, an appreciation of the malformations that will be found makes this unnecessary in most cases. If the lesion is recognized as one of the low types, the perineal anoplasty and pull-through operation can be expected to give a very high percentage of good results, provided there is no fistula into the urinary tract. If the lesion cannot be so identified or if there is a fistula in the upper vagina or urinary tract, the combined abdominoperineal operation offers the best chance of a good result.[8] Thus, there is a roentgenologic problem only when no "fistula" or ectopic anus can

TABLE I

CLASSIFICATIONS OF ANORECTAL ANOMALIES MODIFIED FROM SCOTT AND SWENSON[11]

Scott and Swenson[11]	Ladd and Gross[7]	Browne[3]
Low Level		
Stenosed Anus	Type I	(a) Imperfect anus (mild stenosis) (b) Microscopic anus (extreme stenosis)
Covered Anus	Type III Perineal Fistula	Covered Anus (a) Covered female anus (b) Covered male anus (1) Blue line on perineum (2) Hypospadias or cleft of urethra or fistula of urethra
Ectopic Anus		Ectopic Anus
Perineal	Type III	Shotgun perineum
Vulval	Type III	Vaginal ectopic anus
Male urethral	Type III	Male ectopic anus
	Perineal Fistula Vaginal Fistula	
Congenital Cloaca	Type III	
Rectal Atresia	Type IV	
High Level		
Imperforate Anus with: Rectourethral fistula Rectovesical fistula No fistula High rectovaginal fistula	Type III	Rectal Agenesis Often combined with a true fistula

be detected by physical examination and urinalysis.

REPORT OF CASES

CASE I (DM). This male newborn was seen during the first twenty-four hours of life with an imperforate anus and an anterior perineal fistula. Roentgenograms made with the inverted technique demonstrated the anal dimple to be 3 cm. from the distal end of the rectal pouch. A barium enema study was performed through the "fistula" in the perineum. Fluoroscopic spot roentgenograms (tube film distance [TFD] 20 inches) demonstrated a separation of 2.8 cm. between the distal rectal pouch and the marker in the anal dimple. Using a 40 inch TFD, the distance was 2.4 cm. When the TFD was extended to 6 feet, a measured distance of 1.5 cm. was noted. A voiding cystogram was obtained to exclude the presence of a fistula between the urinary and intestinal tracts.

Comment. The position of the ectopic anus in the perineum was readily visible. The recognition of the ectopic anus or "fistula" as such is sufficient to classify the malformation as a low type. Recognition of the lesion in this case, as in most others, would have completely eliminated the necessity for performing the barium enema examination, the cystography, or, for that matter, any roentgenographic study for determining the surgical approach.

CASE II (RD). A male newborn was admitted on the day of birth with an imperforate anus

and no apparent fistula. Three separate urinalyses showed no evidence of meconium or epithelial debris. Inverted roentgenograms demonstrated the opaque marker 4 cm. from the rectal pouch (Fig. 1). The marker, however, was not at the actual site of the anal dimple. The gas in the rectum extended below the pubococcygeal line. Air was present in the bladder, but was not recognized at the time by the attending or consulting physicians.

A perineal anoplasty and pull-through operation was performed. The operative report stated that a fistula was specifically searched for but not demonstrated.

The patient did well postoperatively and was discharged. Approximately two months later, he was re-admitted because of fecaluria of one day's duration. Excretory urography failed to demonstrate the fistulous connection. Dilatations of the rectum were performed, and the patient was discharged. He returned two months later with a urinary tract infection which responded to treatment. At the age of eighteen months, following cystoscopy and demonstration of the fistula in the posterior urethra, surgical correction was accomplished. The patient has done well except for episodes of fecal impaction which have been treated symptomatically.

Comment. The air in the bladder, although unrecognized, was present on roentgenograms made the first day of life. Appreciation of this finding would have established the diagnosis of a rectourinary fistula in spite of the presence of three negative urinalyses and would have indicated the combined abdominoperineal operation.[8] Had the pubococcygeal line[11] been used as a criterion for the surgical approach, it would have been misleading, because the air in the rectal pouch descended below this line by approximately 4 mm.

Case III (RP). A male newborn with an imperforate anus had inverted roentgenograms which demonstrated a 2.5 cm. distance between the anal dimple and the rectal pouch. It was noted that the pouch descended below the pubococcygeal line by 3 mm. (Fig. 2). A transverse colostomy was performed on the second day of life. The incidental complication of hypertrophic pyloric stenosis was managed by a Ramstedt procedure at the age of four weeks,

Fig. 1. Case II. Inverted roentgenogram demonstrating gas in the rectum 3 mm. below the pubococcygeal line. Arrow indicates air in bladder due to a rectourinary fistula. The selection and placement of the marker is poor.

and the infant did well except for recurrent episodes of upper urinary tract infection. At the age of eighteen months, he was re-admitted for removal of calculi from the left kidney. A rectourethral fistula was discovered during the abdominoperineal anoplasty and was repaired. The colostomy was closed two months later. Follow-up at the age of eight years demonstrated a severe degree of rectal incontinence and chronic pyelonephritis.

Comment. This is one of 4 cases in our series of rectourethral fistulas treated by colostomy which had repeated upper urinary tract infections, even though the distal colon was defunctionalized. In general, colostomy was performed on those patients

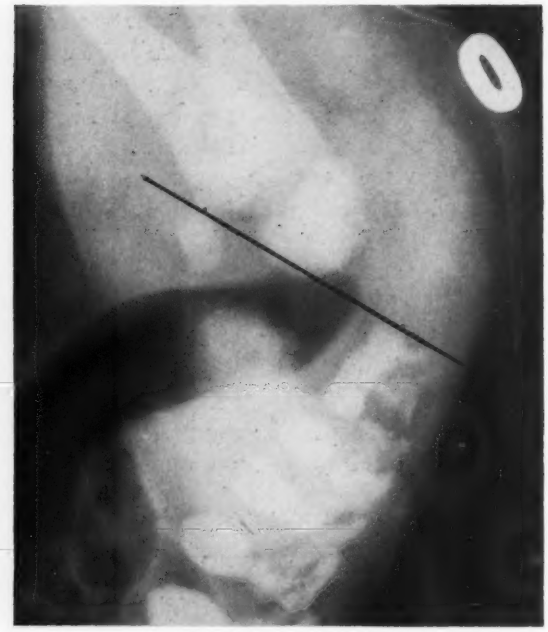

Fig. 2. Case III. The air in the rectum descends 3 mm. below the pubococcygeal line in this inverted roentgenogram.

with the more serious coexisting congenital anomalies, and the morbidity and mortality were high.

Case IV (JV). The Wangensteen-Rice roentgenograms on this newborn male demonstrated the air in the rectal pouch below the pubococcygeal line by 9 mm. (Fig. 3). A perineal anoplasty and pull-through procedure was performed with excellent results.

Comment. Inasmuch as no fistula was ever demonstrated in this child, it is thought that this represented a case of unrecognized microscopic anus or covered anus.

This is one of the situations in which we feel that the Wangensteen-Rice roentgenograms may be helpful; *i.e.*, where no fistula is detectable by clinical or laboratory means, air well below the pubococcygeal line may suggest a low type lesion. Of course, recognition of a microscopic or covered anus[3] would have obviated the need for roentgenograms in this case also.

Case V (BP). The inverted roentgenogram in this newborn male showed the air in the rectal pouch within 4 mm. of the skin (Fig. 4). No fistula could be found, and the patient was operated on from below without complications. A good result was achieved.

Comment. In this infant, there were anomalies of the lumbar spine and sacrum and fourteen pairs of ribs. This is one of the few cases in which there were anomalies of the vertebrae (sacrum and coccyx) which did not have serious complicating malformations. The recognition of this case as a very low lesion allowed the simpler form of treatment.

Case VI (GDB). This female newborn had an imperforate anus and slight abdominal distention at birth. She developed a lower abdominal mass within the first six hours. Physical examination disclosed no anal orifice or urethra, but a small amount of urine was noted coming from the introitus. The child's condition was critical from the time of birth.

Fig. 3. Case IV. Inverted roentgenogram showing air in the rectal pouch 9 mm. below the pubococcygeal line, which is very suggestive of a low malformation.

Inverted roentgenograms of the abdomen demonstrated a "rectal pouch" to be 2.5 cm. from the anal dimple (Fig. 5, *A* and *B*). Within the abdomen a gas and fluid-containing organ, which measured 5 cm. in diameter, was seen to extend across the abdomen and to occupy almost the entire abdominal cavity. Partial agenesis of the sacrum, as well as a minor congenital anomaly of L_4–L_5 was evident. The study was interpreted as imperforate anus with possible volvulus of the sigmoid colon.

Exploratory laparotomy at the age of two days revealed a large mass arising from the pelvis which was thought to be the bladder. A "cystostomy" yielded a large amount of urine. Because of the patient's poor condition, a sigmoid colostomy was performed. The postoperative course was downhill leading to death at the age of nine days.

Necropsy revealed extreme stenosis of the vagina, a bifid uterus and vagina, opening of the urethra into the vagina, and a rectovaginal fistula. In essence, this was a "cloaca" with stenosis of the external opening. The "loop of bowel" seen on the original roentgenogram actually represented a dilated "cloaca."

Fig. 4. Case v. Inverted roentgenogram showing air in the rectum 11 mm. below the pubococcygeal line and 4 mm. from the anal marker. This is definitely a low lesion. Note the hypoplasia of the sacrum.

Comment. This is one of the rare situations which may not be readily apparent after simple clinical and laboratory examinations. Only in rare situations such as this and rectal atresia (Type IV lesions), which few authors have encountered, do we feel that injection of contrast material may be of value in the definitive preoperative evaluation.

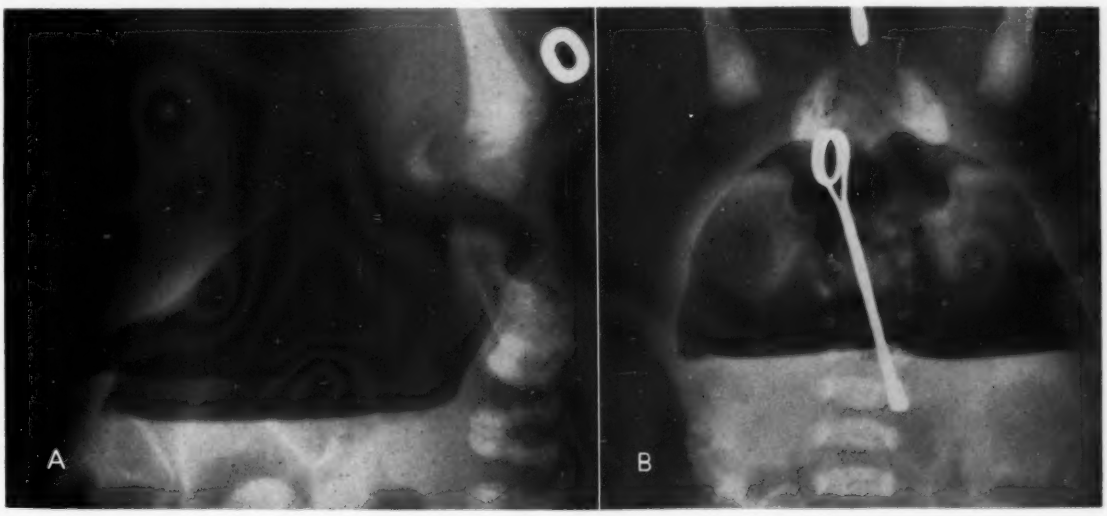

Fig. 5. Case VI. Inverted roentgenograms of abdomen in lateral (*A*) and anteroposterior (*B*) projections demonstrating the large air-fluid containing cavity. This represents a dilated cloaca. Note the anomalies of the lumbosacral spine.

We encountered a case of jejunal atresia that had been misdiagnosed as imperforate anus Type IV. A plain roentgenogram should have been sufficient for the proper diagnosis. Ileal atresia or the meconium plug syndrome could more commonly give rise to confusion because of the difficulty of distinguishing between dilated loops of small bowel and colon on roentgenograms in the newborn period. Demonstration of a microcolon by barium enema would exclude a Type IV "imperforate anus" and clearly point to a small bowel obstruction or the much less likely possibility of total aganglionosis of the colon.

DISCUSSION

We do not completely concur with the belief of Scott and Swenson[11] that rectal gas which extends below the pubococcygeal line is necessarily indicative of a low level lesion. In 4 of our cases the "line" would have been misleading. The fact that the "line" is based on bony landmarks and the malformations are chiefly in the soft tissues probably invalidates it as an absolute criterion.

Conversely, we have found that many lesions of the low type do not show gas below this line. The probable reasons for this are ascribed to the pitfalls mentioned above. We encountered no case in which the gas did not extend below the symphysis-S_2 line of Kjellberg, Ericsson, and Rudhe.[6] We believe that such cases exist but are very uncommon.

The discrepancies, when present, between the surgical findings and the roentgenographic observations, in our series, were most frequently an overestimation of the distance between the rectal pouch and the exterior. Only once was the reverse situation encountered. Actually, the distance itself is of little consequence in most cases.

Most lesions can be accurately diagnosed by clinical observation alone within a few minutes after birth. Greater familiarity with the various malformations encountered would usually indicate the proper choice of treatment and result in decreased mortality and morbidity.

In the female infant there is no need for inverted roentgenograms. Those with visible fistulas are low type lesions. If no fistula can be seen, surgery from above is advisable because of the probability of a high rectovaginal or rectovesical fistula.

In males, inverted roentgenograms can be helpful in some cases where there is no fistula ("anus" or hypospadias) determinable clinically or by urinalysis. First, the demonstration of air in the bladder, as in Case II, indicating a lesion of the high type, would lead to recognition and optimal treatment. Secondly, air extremely close to the perineum might suggest a very low lesion such as anal stenosis or covered anus and lead to its proper management (Cases IV and V). If Type II lesions (Ladd and Gross) actually exist, they would likewise receive proper treatment on this basis.

Frequently, the outcome of a case will be determined by associated conditions such as prematurity and coexisting congenital anomalies. Tracheoesophageal fistulas, congenital heart disease, atretic and stenotic small bowel lesions, urinary anomalies, musculoskeletal dysplasias, and central nervous system lesions may be as serious or more serious than the anorectal malformation.

The demonstration of associated congenital anomalies may affect the choice of operative procedure and is one of the valid reasons for roentgenologic study. Several roentgenograms should suffice for this purpose and they need not be made with the infant inverted.

Following surgery, excretory urography and voiding cystography are recommended to demonstrate congenital abnormalities of the urinary tract and such postsurgical complications as fistula or paralysis of the bladder.[5] More than one-third of our cases had associated urinary abnormalities, either congenital or acquired.

SUMMARY AND CONCLUSIONS

Roentgenograms of the inverted infant are usually not necessary for determination of the anomaly of imperforate anus or its surgical treatment. The various lines and measurements mentioned in the literature have only very rough "rule of thumb" significance and may be misleading. Preoperative contrast studies are rarely indicated.

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CONGENITAL LYMPHANGIOMA*

By P. E. RUSSO, M.D., *and* JAMES P. DEWAR, M.D.
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CONGENITAL lymphangioma is not a common disease. Most often it occurs in the neck and supraclavicular area and is referred to as cystic hygroma. Less often it develops in the axilla or mediastinum and rarely in the omentum and other parts of the body. Our reason for reporting this case is because of the unusual size and location of the tumor. Its site was the lower portion of the abdomen with extension into the upper thigh.

Although surgical removal is considered the best form of treatment for this type of tumor, whenever complete surgical extirpation is not possible or the tumor recurs or spreads, radiation therapy to control the tumor should be tried.

REPORT OF A CASE

This baby was seen on May 5, 1953 when she was seventeen months old. A large abdominal mass which extended into the thigh had been present since birth and had grown larger with the growth of the child (Fig. 1).

The child weighed 27½ pounds and was 31 inches in height. She did not appear to be acutely ill and outside of the abdominal and inguinal mass no other abnormalities were present. A large mass was located in the left lower abdomen and was more than 15 cm. in diameter. It was soft and the overlying skin was discolored as if it had been recently bruised. A smaller mass which was delineated by the inguinal fold extended along the anterior surface of the left leg. The labium majus on the left side was also involved.

A few days after admission to the hospital surgical excision of both masses was performed. Because the tumor mass surrounded the saphenous vein, this structure had to be ligated and severed at its insertion into the femoral vein. The tumor mass contained numerous sacculations and cavernous sinuses which were mostly filled with lymph and a small amount of old blood. It was noted that there was extension of the tumor into the fascia of the external oblique muscle and the rectus sheath. As much of this tissue was removed as possible and the incision was closed by primary suture.

The patient was re-admitted on November 9, 1953 because of a cauliflower like growth 6×3 cm. in size present in the inguinal area and extending into the left labium majus (Fig. 2). A biopsy of this mass showed recurrent tumor. Surgical exploration and excision was attempted a few days later. At this time it was found that the mass involved all the structures in the inguinal canal and penetrated deeply below the fascia of the muscles of the thigh. Upward exploration showed lymph sacculations extending as far as the subcostal margin on the left side. As much of the mass as possible, including the overlying skin, was removed and the defect covered with a large skin graft.

Only a month later it became evident that recurrence of tumor was taking place about the scar and surrounding skin (Fig. 3). Biopsy again showed the same microscopic appearance (Fig. 4).

Radiation therapy was considered for control of this tumor and was started on February 19,

FIG. 1. May 6, 1953. Photograph showing the size and location of the tumor.

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Fig. 2. June 15, 1953. Photograph showing recurrence of tumor within center and along scar margins four weeks after first surgical excision.

1954. Conventional therapy, 200 kv. and Thoraeus filter with portals 15×15 cm. in size were used, two anterior and two posterior, delivering a total dose of 600 r measured in air in a period of eight days. A second series of roentgen treatments was given six weeks later, again each field receiving a dose of 600 r. A third and final series of treatments was given only to the inguinal area six weeks later where there was still some clinical evidence of residual tumor. It was evident by this time that satisfactory response of this tumor to irradiation had been accomplished (Fig. 5).

Gross Pathology. The original specimen consisted of two ellipses of skin with underlying tissue connected together at a 90 degree angle. The ellipses of skin measured 11×3.5 and 12×4 cm. through the center point. In addition, two other pieces of skin and subcutaneous tissue measuring 11×4 cm. and 5×4 cm. were examined. The various specimens measured up to 5 cm. in thickness. The under side of these specimens showed numerous cavernous spaces measuring up to 3 cm. in diameter lined by a shiny thin membrane. Those that were still intact contained a serosanguineous fluid. Multiple sections revealed numerous small spaces lined by the same type of shiny membranes. None of these appeared to contain blood. The skin itself appeared uninvolved. Six and one half months later, another specimen consisting of a large sheet of skin and attached subcutaneous adipose tissue and measuring 17.5×14

Fig. 3. February 17, 1954. Photograph showing recurrence of tumor over entire skin graft and along the edges following a second attempt to remove it by radical surgery.

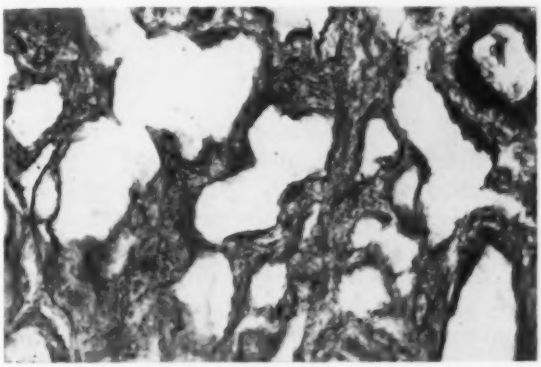

Fig. 4. Photomicrograph showing histologic appearance of the tumor.

Fig. 5. December 6, 1954. Photograph showing control of recurrence and spread of tumor ten months after radiation therapy.

cm. was examined. At this time several lymph nodes were also present. In the center of the specimen, numerous cyst-like structures were seen, similar to those noted in the previous specimen. Several nodular firm areas were noted which contained scar tissue.

Microscopic Findings. The microscopic appearance was similar in the original and subsequent specimens. In both cases an intact surface epithelium and dermis were noted. The underlying subcutaneous tissue contained small and large spaces, many of which were filled with a pale eosinophilic material. The lining cells formed a single layer, and were flat and elongated. The surrounding tissue consisted of loose fibrous connective tissue. Small and large areas were noted. In several places foci of lymphocytes were present. In general, the structure was well vascularized and several small and fairly large blood vessels were also seen. Figure 4 shows a typical area. The lymph nodes showed a reactive lymphoid hyperplasia. The specimen included skin, subcutaneous tissue from the left lower quadrant, left thigh including the labium majus and left and right inguinal lymph nodes.

COMMENT

This case has now been followed for a period of over six years. Satisfactory control of the tumor has been accomplished. The skin graft showed good tolerance to the radiation. In all other respects this child has shown normal growth and development. Recent roentgen studies of her skeleton showed only a slight asymmetry between the left and right innominate bones with slight underdevelopment of the left side. We were aware of the fact that radiation injury to the female reproductive organs could not be avoided; however, in this case we believe it was a life saving procedure. Although radiation therapy is being used less and less in this era for benign conditions, in this particular case the results were most gratifying.

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We wish to thank Dr. J. R. Riggall for his interest and his help in following this case for these many years.

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LYMPHOSARCOMA IN CHILDHOOD*

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THE pessimism regarding the prognosis of many malignant tumors of childhood has diminished considerably in the last ten years. Lymphosarcoma, however, perhaps because of the apparent relationship with some leukemias, is still often erroneously accorded the same hopeless prognosis of leukemia. There are increasing numbers of references in the literature[1–4] attesting to long survivals of children suffering from lymphosarcoma, and the Memorial Hospital experience also demonstrates that all such patients should not be dismissed as incurable.

MATERIAL

The present series of 75 cases includes children admitted to the Pediatric Service of Memorial Hospital between 1926 and 1959, some of whom have been previously reported, as well as some of those seen in the author's practice.

There were 57 males and 18 females, a ratio of 3:1. The ages ranged from one year to fourteen years. There were 41 cases of lymphocytic lymphosarcoma, 31 instances of reticulum cell sarcoma, and 3 of follicular lymphosarcoma (Fig. 1).

CLINICAL SITES AND SYMPTOMS

The most frequent initial clinical site, by a considerable margin, was in the abdomen and retroperitoneal region (Fig. 2). Pain (25 cases) and swelling or tumefaction (29 cases) were the most common presenting symptoms. Complaints of asthenia, weight loss, fever, and anemia were quite rare during the course of the disease in most of the children. Symptoms referable to the respiratory and gastrointestinal tracts were also rather uncommon considering the relative frequency of involvement of these systems.

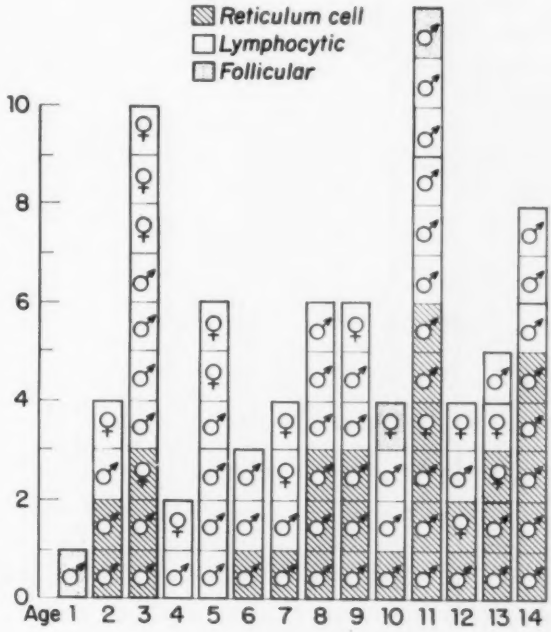

FIG. 1. Distribution of 75 cases of lymphosarcoma by age, sex and histologic type.

THERAPY AND RESULTS

Surgery alone was used in 8 patients, surgery and roentgen therapy in 8, and roentgen therapy alone in 21. The following forms of chemotherapy were utilized: methotrexate in 22, meticorten in 8, nitrogen mustard in 8, actinomycins in 3, 6-mercaptopurine in 2, and Coley's toxins in 4. Chemotherapy was also given in conjunction with or following conventional therapy in a total of 38 of the children.

There are 21 survivors among these 75 patients, 15 of whom are living over five years since onset of the disease. Five of these children are living over ten years, 2 over fifteen years, and 1 of them more than twenty years without evidence of disease. Three of the 15 children had follicular lymphosarcoma, 6 reticulum cell sarcoma,

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TABLE I

15 LYMPHOSARCOMA CASES SURVIVING OVER FIVE YEARS

Case	Sex	Age	Admission	Onset of Symptoms Prior to Admission (mo.)	Histologic Type	Site	Treatment	Latest Follow-up Date	Survival with No Evidence of Disease (yr.)
1 W.B.*	M	14	1937	8	reticulum	scapula	Coley's toxins, roentgen therapy	5/59	21
2 A.A.*	F	12	1940	4	reticulum	bilateral cervical	surgery, roentgen therapy	1/60	19
3 J.M.†	M	3	1946	3	lymphocytic	right parotid	Coley's toxins, roentgen therapy	1/60	13
4 J.C.*	F	13	1943	2	reticulum	fibula	surgery, roentgen therapy	3/56	13
5 S.S.†	F	5	1948	3	lymphocytic	cervical and uterus	surgery, roentgen therapy	1/60	11
6 S.B.	M	1½	1950	1	follicular	axillary and inguinal	surgery	1/60	10
7 R.S.*	M	12	1951	24	lymphocytic	cervical and axillary	roentgen therapy	8/57	9
8 G.C.*	M	11	1951	1	follicular	cervical	surgery	7/59	8
9 A.B.*	F	10	1952	72	follicular	tonsils	roentgen therapy	2/60	7
10 D.F.*	M	14	1953	3	reticulum	humerus	nitrogen mustard, roentgen therapy	1/60	7
11 S.K.	M	11	1953	3	reticulum	femur	Coley's toxins, nitrogen mustard, roentgen therapy	1/60	6
12 R.J.*	M	6	1953 1954	8	lymphocytic	cervical	roentgen therapy, methotrexate	1/60	6
13 S.H.†	M	3	1954	2	lymphocytic	nasopharynx	roentgen therapy, methotrexate	1/60	5
14 R.L.†	M	8	1954	2	lymphocytic	inguinal	roentgen therapy, methotrexate	1/60	5
15 L.S.†	M	11	1954	3	reticulum	cervical	surgery, meticorten, methotrexate	1/60	5

* Reported previously by Rosenberg, Diamond, Dargeon, and Craver.[4]
† Reported previously by the present author.[2]

and 6 lymphocytic lymphosarcoma (Table 1). Of the other 6 patients, 5 are living between three and five years from the onset of their illnesses, but 2 have shown moderate activity of the disease at intervals. Of the 15 children surviving over five years, 6 received chemotherapy and 3 had Coley's toxins as well as surgery or irradiation.

In addition to these 75 patients whose intitial and present diagnosis is lymphosarcoma, there were 21 other children admitted whose primary diagnosis was lymphosarcoma, but who subsequently developed leukemia (Table 11). In all but 1 this complication occurred less than twenty months following the initial lymphosarcoma diagnosis. In this case, the lymphosarcoma was never quiescent for more than a few weeks during a period of four years and the leukemia developed two weeks before death.

It has been recognized and previously

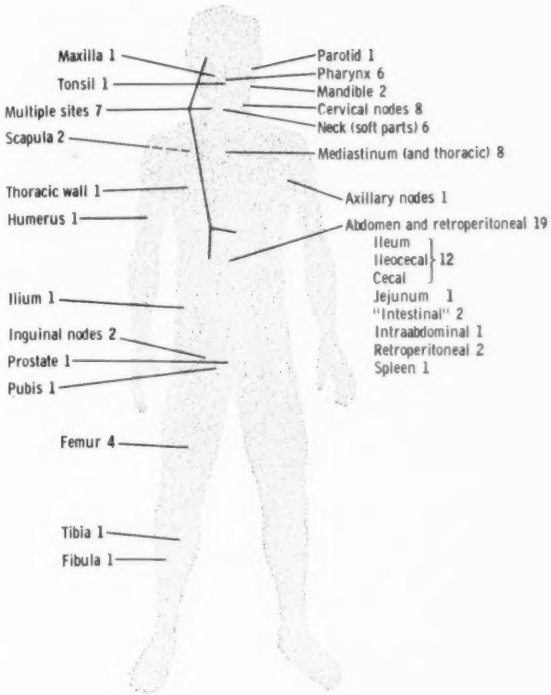

FIG. 2. Distribution of the presenting clinical sites in 75 cases of lymphosarcoma.

acknowledged that the introduction of another therapeutic modality, the action of which in any specific case cannot be determined exactly, denies appraisal of the natural history of the disease and the effects produced by either surgery or irradiation, alone or in combination. The serious nature of this disease, however, from a clinician's standpoint, appeared to warrant an attempt to improve the prognosis by using the compounds which are known to produce at least temporary regression in some lymphosarcomas as well as the frequent concomitant or complication of the disease; namely, leukemia.

From 1926 to 1951, 5 patients were so treated. Three received nitrogen mustard but had fatal terminations. Two received Coley's toxins in addition to conventional therapy; one of them is a thirteen year and the other a twenty-one year survivor.

In the 1951 to 1959 group, 38 children have received different chemotherapeutic agents as well as roentgen therapy and surgery. These patients were unselected. Many had widespread disease when referred to Memorial Hospital and were in an actual or quasi-terminal state. Twenty-four have expired, 5 of whom developed leukemia from one to nine months after the initial diagnosis of lymphosarcoma was made. Fourteen are living, all over two years. None of these children show leukemia, but 2 of them, as mentioned above, have occasional signs of activity of their lymphosarcomas.

Our current plan is to administer nitro-

TABLE II

21 CASES OF LEUKOSARCOMA

Sex	No.	Age (yr.)	No.	Initial clinical site	No.	Initial symptom	No.	First symptom to diagnosis		Diagnosis to evidence of leukemia		Survival from onset of first symptom	
								No.	mo.	No.		mo.	No.
M	16	<1	2	cervical	6	swelling	15	4	<1	1		1	1
F	5	2	2	inguinal	2	pain	4	8	1	2		2	1
		3	3	scalp	1	cough	1	4	2	2		4	2
		4	2	mediastinum	6	dysphagia	1	2	2	3		5	3
		5	2	parotid	1			2	4	4		6	3
		6	4	mandible	3			1	5	2		7	2
		7	1	scapula	1				6	3		8	2
		8	2	testis	1				8	2		9	2
		9	1						9	1		10	1
		10	2						48	1		11	2
												19	1
												48	1

gen mustard (0.4 mg./kg.) as soon as the child's condition permits following the definitive therapy, whether it be surgery, irradiation or both. This interval may be a day or several weeks.

Subsequent to the administration of nitrogen mustard, the patient is observed for hematopoietic depression. Usually between two and six weeks elapse, after which methotrexate (0.625 mg. to 2.5 mg.) is begun. The dose is regulated to keep the hemoglobin above 9.0 gm. per cent and the total leukocyte count at 4,000–6,000 per mm^3.

The drug is given daily for not less than one year. If, at this time, there is no evidence of disease, the drug is given in cycles of three weeks on and one week off.* The periods of "off therapy" have been gradually extended, but an attempt is made to maintain most of the children on this routine for three years.

Obviously, it would be incorrect at this time to assume that the usual modalities of surgery and roentgen therapy need any supplementary assistance from chemotherapeutic agents. However, this procedure has been presented because the numerical limitations in the experience of any single institution will necessarily preclude a statistically accurate appraisal of its value for a considerable period of time. It is our intention to continue to explore this method and we hope that we have an opportunity of exchanging experiences with others who may also try it.

* The cyclic program was developed because we have found, in treating some children suffering from disseminated reticuloendotheliosis, that prolonged antifolic therapy, if given in such cycles, controlled the disease in many instances but did not produce drug toxicity or discernible clinical defects.

SUMMARY

A series of 75 children with lymphosarcoma and 21 additional juvenile patients with a primary diagnosis of lymphosarcoma and the later development of leukemia in the course of their illness is reviewed.

The survival rate (15 living over five years) emphasizes the previously known fact that this is not only not an incurable disease in the young but that it actually has a better prognosis than many other cancers.

The results obtained with the use of chemotherapeutic agents, supplementing surgery and irradiation, are described. It is believed that encouragement for further study of this method of management has been demonstrated.

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NEUROBLASTOMA: REVIEW OF TWENTY-EIGHT CASES AND PRESENTATION OF TWO CASES WITH METASTASES AND LONG SURVIVAL*

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NEUROBLASTOMA in children presents a most interesting and unpredictable disease. It can have all the accepted criteria of a malignant tumor, namely, cellular proliferation, invasiveness, and metastases, producing ultimate death, yet there are reports of spontaneous cures.[7,8,17]

A great deal has been written on this subject during the past eight decades. Virchow,[33] who first recognized the neural origin of neuroblastomas in 1864, referred to it as a glioma. For several decades after that, these tumors were called sarcomas or lymphosarcomas. In 1891, Marchand[20] described the similarity of the tumor cells to those in the developing central nervous system of embryos. Pepper (1901)[24] reported 6 cases of "congenital sarcoma of the suprarenal gland" with metastases to the liver (Pepper type). Hutchinson (1907)[15] reported 10 cases with metastatic disease to the skull and orbit (Hutchinson type). Wright (1910)[36] presented a classic paper in which he confirmed the similarity of the rosettes and fibril bundles to those in embryonal adrenal and sympathetic ganglia. He suggested the term neuroblastoma. Herxheimer (1914)[13] demonstrated that the fibrils were primitive nerve fibers and arose from the cells of the tumor (neuroblasts).

Prior to 1930 there were sporadic reports of cures, but, in general, the tumor was considered to be almost always fatal. Since then, the reported cure rate has risen substantially with the use of surgery and radiation therapy. We would like to report our experience with 28 cases of neuroblastoma and present 2 cases with extensive metastatic disease and long term survival.

HISTOPATHOLOGY

The neuroblastoma is a typical example of a malignant embryoma, which implies that the tumor arises as a result of maldevelopment or dysontogenesis of embryonal neuroblasts derived from the primitive neural crest ectoderm. This embryonal tissue normally differentiates into the spinal and sympathetic ganglia as well as the chromaffin tissue of the adrenal medullae and periaortic bodies of Zuckerkandl. Dysontogenesis of this tissue may be manifested as a disturbance in the normal rate of maturation or differentiation of the primitive neuroblasts, with subsequent overgrowth of these cellular elements into a tumor mass. If these tumors are the result of dysontogenesis, it is not known whether the tumor cells are essentially normal neuroblasts which have failed to properly differentiate, or whether these cells have undergone a malignant transformation.

The neuroblastoma tumors vary considerably in their histologic appearance depending upon the relative degree of maturation attained by the constituent neuroblasts. On this basis, arbitrary separation into morphologic types is undertaken, and this has been done in this study.

Sympathicoblastoma. This is the most primitive form and is composed of fairly uniform sheets or perivascular masses of primitive neuroblasts (Fig. 1). Rosette or pseudorosette formation is not prominent, and neurofibrillary processes associated with the cells are barely, if at all, discernible.

Neuroblastoma sympatheticum. When a somewhat greater degree of differentiation is present, the picture of the classic neuro-

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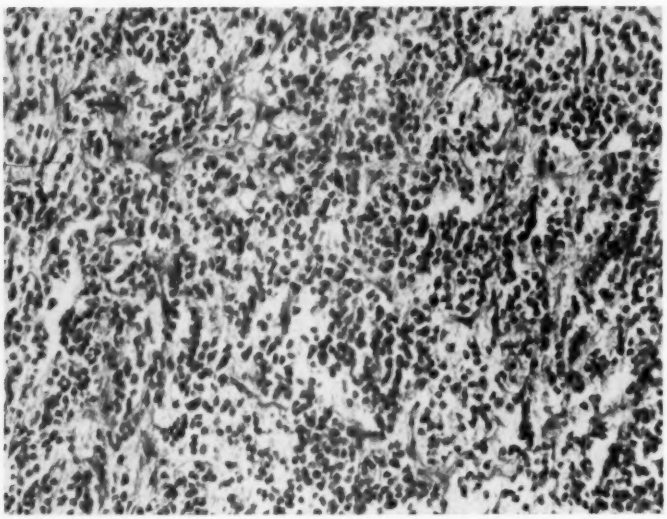

Fig. 1. Sympathicoblastoma. This microscopic section (H&E stain) shows numerous small sympathicoblasts supported by a delicate fibrovascular stroma. Neurofibril and rosette formation are not prominent.

blastoma sympatheticum is encountered (Fig. 2). Cytologically, this lesion is similar to the sympathicoblastoma, but definite eosinophilic, neurofibrillary processes are seen in relation to the cells, and characteristic rosette or pseudorosette formation is present to a variable extent. The rosette is characterized by a peripheral ring of neuroblastic cells with a central core of eosinophilic neurofibrillary processes.

Ganglioneuroblastoma. This term is used to describe the lesion in which more advanced maturation has occurred (Fig. 3). Neurofibril formation may be very abundant. Large neurofibrillary lakes are commonly seen bordered by septa of neuroid connective tissue. In and around the neurofibrillary foci are variable numbers of neuroblasts, similar to the cells seen in less mature lesions (Fig. 4). It is possible to see

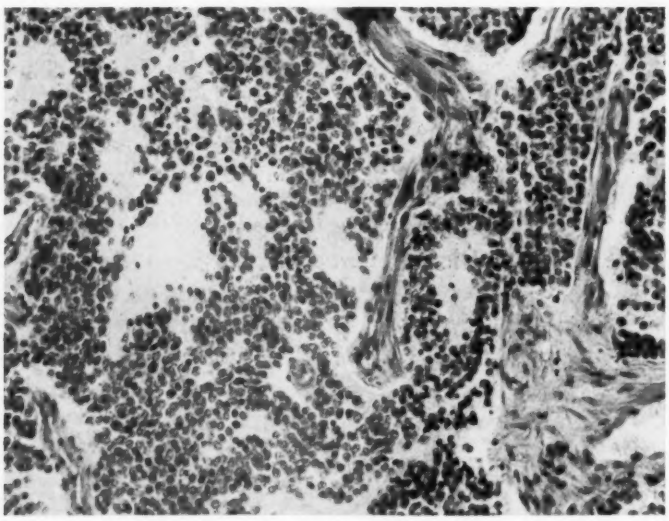

Fig. 2. Neuroblastoma. Photomicrograph (H&E stain) showing fairly typical neuroblastoma. The embryonal neuroblasts pallisade around masses of neurofibrillary processes to form rosettes or pseudorosettes. The cells tend to be slightly larger than in the sympathicoblastoma.

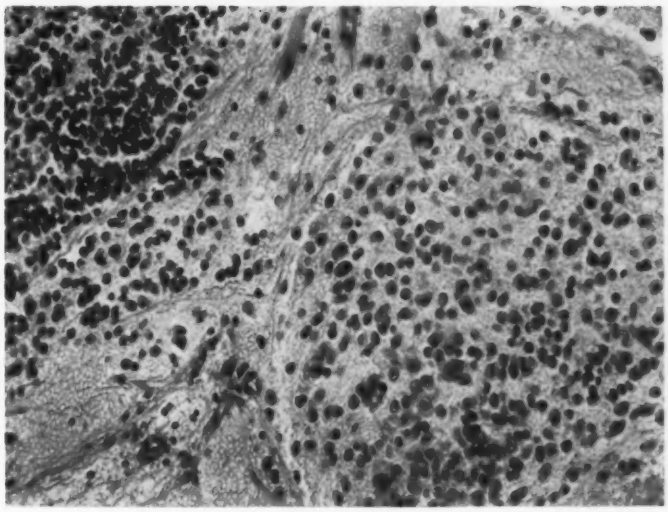

FIG. 3. Ganglioneuroblastoma. This photomicrograph (H&E stain) shows within areas of dense neurofibril formation, clusters of cells varying from the primitive sympathicoblast to virtually mature ganglion cell.

areas within this tumor which are morphologically indistinguishable from ganglioneuroma in which mature ganglionic cells are embedded within a neuroid connective tissue stroma (Fig. 5). The foci of immature neuroblasts exclude this diagnosis.

It is obvious that no sharp divisions are present between these morphologic categories. A continuous spectrum of neuronal maturation is apparent from the sympathicoblastoma to the ganglioneuroma. Completely mature ganglioneuromas have not been included in this study.

CLINICAL MATERIAL

There have been 28 cases of neuroblastoma seen at University Hospitals of Cleveland since 1942. Surgical specimens of all of the cases were reviewed and the diagnosis verified. If confirmation of the diagnosis was not possible, as may occur when Ewing's tumor or other small cell

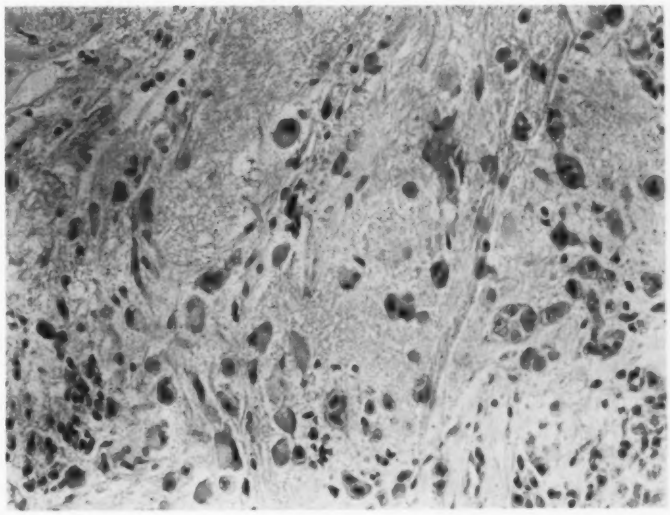

FIG. 4. Ganglioneuroblastoma. Photomicrograph (H&E stain) of an area of a ganglioneuroblastoma which has a greater preponderance of more mature ganglion cells. These cells, none the less, are dysplastic, and show evidence of mitotic activity.

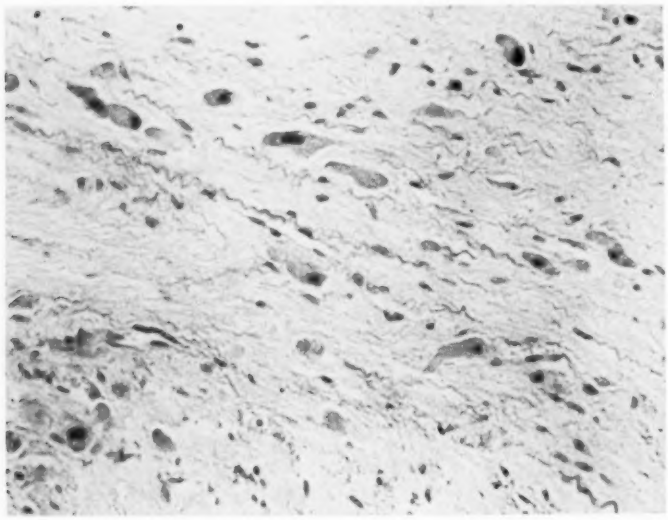

Fig. 5. Ganglioneuroblastoma. Photomicrograph (H&E stain) of an area from the ganglioneuroblastoma depicted in Figures 3 and 4 which is indistinguishable from a mature ganglioneuroma. The ganglion cells are mature and quiescent, and are embedded in a neurofibroma-like stroma.

sarcomas exist as possibilities, the cases were discarded. Definite follow-up was obtained on all of the patients (Table 1).

There were 13 males and 15 females in the series. The age distribution at the time of diagnosis ranged from newborn to four and one half years (Fig. 6*A*). Five of the patients were in the newborn period (birth to one month), 3 having had the disease at the time of birth. Two had metastatic nodules involving the skin, and 1 had a left abdominal mass palpated at birth.

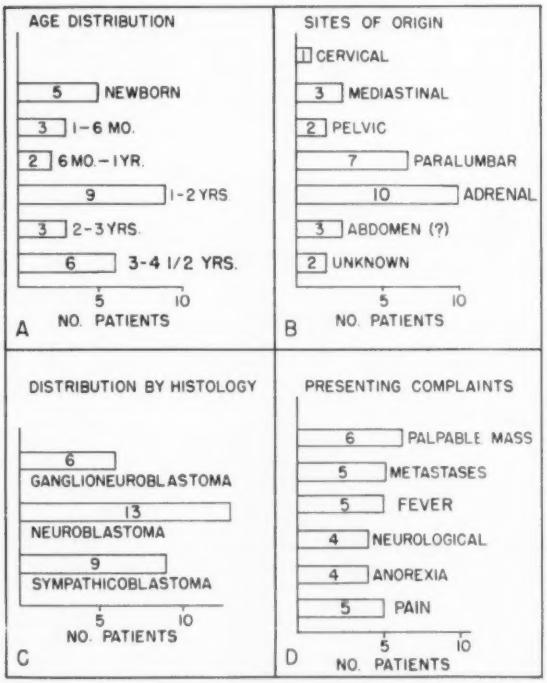

Fig. 6. Chart demonstrating the distribution of patients according to: (*A*) age, (*B*) sites of origin, (*C*) histology, and (*D*) presenting complaints.

The sites of origin could be determined with certainty in only 23 of the 28 patients (Fig. 6*B*). In the 5 of unknown site, 3 arose in the abdomen in close proximity to the adrenal gland, but it could not be determined whether they arose from the adrenal gland or the paralumbar sympathetic chain. Primary sites in the abdominal retroperitoneal sympathetic chain or the adrenal gland were noted in 20 of the 28 patients (72 per cent).

The diagnosis in each case was made by biopsy of either the primary tumor or a metastatic lesion. Classification into the three histologic types was: ganglioneuroblastoma 6, neuroblastoma 13, and sympathicoblastoma 9 (Fig. 6*C*). Bone marrow aspirations were done on 10 patients, of which 5 revealed abnormal cells.

The presenting complaints of the children are tabulated in Figure 6*D*. The disease often presented in such a way that the patients were treated for other illnesses

TABLE I

CLINICAL FEATURES OF 28 PATIENTS WITH NEUROBLASTOMA

Patient	Sex	Age	Primary Site	Histology*	Bone Marrow Examination	Surgery	Radiation Dose†	Metastases	Present Status		
									Living	Dead	Survival
SM	F	17 mo.	adrenal	G		partial extirpation	3,700 r	skull, tibia, ulna	+		6 yr.
WT	M	4 mo.	adrenal	N	+(?)	partial extirpation	none	skull, long bones, skin		+	4 da.
RW	F	newborn	adrenal	N		partial extirpation	3,040 r			+	6 mo.
LH	F	4½ yr.	adrenal	N	+	partial extirpation	4,080 r	skull, long bones, mediastinum		+	3 mo.
MB	F	4 yr.	adrenal	N		biopsy	none	skull, long bones, orbit		+	2 mo.
RB	F	4½ yr.	adrenal	S	+	biopsy	2,070 r	skull, long bones, skin		+	5 mo.
TF	M	4 yr.	adrenal	S		biopsy	none	long bone		+	4 mo.
AC	M	1 yr.	adrenal	S		partial extirpation	3,230 r	liver		+	2 mo.
RD	M	1½ yr.	adrenal	S		partial extirpation	2,100 r	skull, liver, mediastinum		+	1 mo.
AJ	M	4½ yr.	adrenal	N	+	biopsy	3,500 r	skull, long bone, skin		+	6 mo.
DV	M	newborn	cervical	N		partial extirpation	1,750 r	subcutaneous thigh	+		2 yr.
JS	M	5 mo.	mediastinal	N		partial extirpation	2,900 r		+		13 yr.
BB	F	5 mo.	mediastinal	N		biopsy	4,500 r		+		13 yr.
AN	F	3 yr.	mediastinal	G		partial extirpation	2,900 r		+		10 yr.
DH	F	14 mo.	lumbar	G	negative	partial extirpation	2,600 r		+		1 yr.
TF	M	4½ yr.	lumbar	G		partial extirpation	2,300 r		+		1 yr.
ED	F	15 mo.	lumbar	N		biopsy	2,640 r		+		8 yr.
CC	M	1 yr.	lumbar	S	negative	partial extirpation	2,900 r	pelvic lymph nodes	+		4 yr.
SM	F	15 mo.	lumbar	N		partial extirpation	3,430 r		+		3 yr.
MS	F	16 mo.	lumbar	G		biopsy	3,500 r		+		2 yr.
FG	F	3 yr.	lumbar	S		biopsy	2,160 r	mediastinum	+		17 yr.
RD	M	newborn	pelvic	N		partial extirpation	3,700 r		+		4 yr.
PM	M	15 mo.	pelvic	G?		partial extirpation	1,740 r		+		10 yr.
MD	F	newborn	unknown	N	+	biopsy	1,130 r	orbit, long bone, skin		+	1 mo.
LB	M	3 yr.	unknown	N	negative	biopsy	none	orbit, skull, long bone, liver		+	5 mo.
RE	F	1½ yr.	unknown	S		biopsy	2,640 r	skull		+	3 mo.
SH	F	21 mo.	unknown	S	negative	partial extirpation	1,300 r	skull, lung, long bone		+	1 mo.
D I	M	newborn	unknown	S	negative	biopsy	none	skin, liver	+		8 yr.

* G = ganglioneuroblastoma.
N = neuroblastoma.
S = sympathicoblastoma.

† This represents only radiation to the presumed primary site. Radiation doses to metastatic lesions are not recorded.

such as acute rheumatic fever, upper respiratory and gastrointestinal infections, or orthopedic problems. Four presented with neurologic abnormalities: 1 with Horner's syndrome, 1 with blindness, and 2 with spinal cord compression.

Metastatic disease was present in 9 cases when first seen. Metastases developed during treatment in 7 other patients. The distribution of metastases was as follows: bone 11, liver 4, skin 4, mediastinal lymph nodes 3, meninges 2, and lung 1.

ROENTGEN FINDINGS

Roentgenologic examination is undoubtedly the most useful diagnostic aid.[16,28] Of the 20 cases with abdominal tumors, 19 had intravenous urography performed. The urograms were abnormal in 18 cases. Suprarenal tumors usually depressed the kidney down, anteriorly or laterally. There was minimal distortion of the calyceal system, in contradistinction to Wilms's tumors. The remaining paravertebral tumors deviated the ureters medially and anteriorly. Calcification in the tumor was seen in 7 cases (25 per cent). It tended to be rather dense and flocculent. No calcification was seen in metastatic lesions or tumors outside of the abdomen. It is of interest that, in every case with calcium present, there was always residual calcium present after surgery, implying incomplete removal of the tumor.

TREATMENT

The preferred treatment of neuroblastoma is a combination of complete surgical removal of the tumor followed by radiation therapy to the tumor bed. The primary tumor often involved great vessels, major nerves, regional lymph nodes, adjacent viscera and vertebral bodies. Thus, in none of our cases was complete surgical removal possible. Extensive surgical measures to remove all of the tumor are not indicated unless all of the neoplasm can be extirpated without serious damage to abdominal viscera. Partial excision of the tumor was performed in 16 cases, while biopsy only was performed in 12 cases. At surgery, metal clips were used to outline the extent of the tumor. This procedure facilitated positioning the radiation fields.

Twenty-three of the 28 cases received radiation therapy to the primary tumor site, instituted as soon as possible after surgery. The radiation was delivered through opposing ports with daily doses of 200 to 300 r to alternate fields large enough to include all known tumor. A total absorbed dose of 3,000 to 3,500 rad was usually given in a single course requiring about four weeks. The contemplated dose was not achieved in several patients because of marked hematopoietic depression, debilitation, or death of the patient. Occasionally, a higher tumor dose was delivered when the anticipated response was not apparent. Although supervoltage radiation is available, it has not been necessary to employ this modality routinely, since these tumors are sensitive to moderate doses of radiation.

Irradiation of metastatic lesions will afford temporary palliation. The objective is to control the size of the metastatic lesions, thus relieving secondary pressure effects, deformity, and pain. Moderate doses, on the order of 1,000 to 1,500 rad, have been satisfactory. Although we have had no experience with irradiation of hepatic metastases, Farber *et al.*[10] report excellent results with a 66 per cent survival rate.

RESULTS

Neuroblastoma presents a difficult natural history to evaluate. There are reports in the literature of death ten to fifteen years after the initial therapy and presumed cure, but this is unusual. In this series, all of the deaths occurred within six months of diagnosis. Farber *et al.*[10] report that 99 per cent of the deaths in their series occurred within two years of diagnosis. It would seem reasonable, therefore, to report our results in terms of two year survivals.

There are 15 patients living one to seventeen years after diagnosis, an over-all survival rate of 54 per cent. Twenty-six of the patients have been followed two years or longer, and the survival rate is 50 per cent. These figures compare favorably with those found in the literature (Table II).

Survival can be correlated with site of origin, age, histologic type, the presence or absence of metastases, and the type of therapy. Two patients who have not been followed two years will be included, since both had ganglioneuroblastomas and are free of disease at the present time (surviv-

Table II

SURVIVAL NOTES COMPARED WITH THOSE IN THE LITERATURE

Author	Year	No. of Patients	No. of Survivals	Per Cent	Duration
Beck and Howard[2]	1951	475	47	10	?
Snyder *et al.*[29]	1951	24	3	12.5	3 yr.
Oberkircher *et al.*[23]	1953	20	2	10	5 and 15 yr.
Seaman and Eagleton[27]	1953	19	5	26	3 yr.
Charache[4]	1954	10	2	20	9 and 12 yr.
Uhlmann and von Essen[31]	1955	20	7	31	2 yr.
Koop *et al.*[19]	1955	39	12	31	14 mo.
Reiquam *et al.*[26]	1956	18	5	28	14 mo.
Ware[34]	1956	80	7	9	1 yr.
Stowens[30]	1957	105	14	13	1.5 yr.
Knox and Pillers[18]	1958	126	14	11	2 yr.
Farber *et al.*[10]	1959	170	43	25	2 yr.
Dargeon[6]	1960	108	15	13	5 yr.
Present Authors	1960	26	13	50	2 yr.
Totals		1,240	189	15	

ing fifteen months and sixteen months, respectively). Based on past experience, these patients have a good prognosis.

Site of origin. There were 10 cases of tumors proved to be of adrenal gland origin. Of these, only 1 has survived (10 per cent). There were 13 of definite extra-adrenal origin, all of whom have survived. Only 1 of the 5 patients whose primary site remained unknown has survived two years.

Age. There did not seem to be any correlation of survival with age. Others have reported a better prognosis for the younger patients.[10,6] There were 10 patients under the age of one year, 6 of whom have survived (60 per cent). Those patients over one year of age totalled 18, with survival of 9 (50 per cent).

Metastases. If metastatic disease was present at the time of diagnosis, only 1 out of 9 survived (11 per cent). If no metastatic disease was present initially, 15 out of 19 survived (74 per cent). Of this latter group, 7 developed metastases later, with survival in 4 (57 per cent). Thus, the survival in the presence of metastatic disease was 5/16 (31 per cent) compared to a survival rate of 90 per cent (11/12) in those without metastatic disease. The 1 death in the group without metastases was primarily a surgical death (renal vein thrombosis).

Type of therapy. Correlated survival results are as follows: (1) biopsy only: there were 4 in this group, 1 of whom survived (25 per cent); (2) biopsy plus radiation therapy: there were 8 patients in this group, of whom 3 have survived (38 per cent); (3) partial excision plus radiation therapy: there were 15 patients treated in this manner with survivals in 11 (73 per cent).

There were no instances of complete removal of the tumor surgically. There was 1 instance of partial excision without radiation therapy. However, the patient expired before radiation therapy was instituted.

These data are summarized in Table III. Since this series is composed of a rather small number of patients, conclusions of statistical significance may not be drawn, but trends in a particular direction may be indicated.

REPORT OF CASES

Case 1. S.M., a seventeen month old white female, was first admitted to University Hospitals on November 30, 1953 with a mass in the right side of the abdomen extending from the costal margin to the iliac crest. Roentgeno-

TABLE III

SURVIVAL RELATED TO VARIOUS PARAMETERS

		Total	Survivals	
			No.	Per cent
Age	Under one year	10	6	60
	Over one year	18	9	50
Site of Origin	Adrenal	10	1	10
	Extra-adrenal	13	13	100
	Unknown	5	1	20
Histologic Type	Ganglioneuroblastoma	6	6	100
	Neuroblastoma	13	6	46
	Sympathicoblastoma	9	3	33
Metastases	Present at diagnosis	9	1	11
	Present later	7	4	57
	Total with metastatic disease	16	5	31
	No metastatic disease	12	11	90
Type of Therapy	Biopsy only	4	1	25
	Biopsy plus radiation	8	3	38
	Partial excision plus radiation	15	11	73
	Partial excision only	1	0	0

graphic studies of the chest and long bones were negative. Urinary tract roentgen studies demonstrated a right suprarenal soft tissue mass containing calcium (Fig. 7, *A* and *B*). On December 2, 1953 an exploratory laparotomy revealed a 12×12 cm. tumor occupying the entire right flank. The regional lymph nodes about the aorta and along the root of the mesentery were involved. Partial resection of the tumor was performed and microscopic examination revealed a ganglioneuroblastoma of the right adrenal gland.

The patient was given radiation therapy to the right upper abdomen through alternating anterior and posterior ports with 250 r (air) daily at 50 cm. focal skin distance, 220 kv., and 0.5 mm. Cu and 1.0 mm. Al filtration. A central tissue dose (CTD) of 3,700 r was given without complication except for a mild scoliosis subsequently (Fig. 7, *C* and *D*).

On January 29, 1954 metastatic lesions were noted in the right frontoparietal region (Fig. 8, *A* and *B*). On February 27, 1954 another area of metastatic disease was found in the right tibia (Fig. 9 *A*). Two bone marrow aspirations were negative. Radiation therapy was given to the skull and tibia with 2,400 r (air) and 200 r (air), respectively. The patient did well until early 1955 when she developed anorexia and weight loss. A metastatic lesion was noted in the left ulna on January 20, 1955 (Fig. 10*A*) which, on biopsy, proved to be tumor. However, there was more fibrosis and the lesion was less cellular and more differentiated than the original biopsy specimen. Radiation therapy was given to the ulna totaling 1,200 r (air).

The patient was last seen in December, 1959. She has done very well with no evidence of recurrence (Fig. 7, *C* and *D;* 8, *C* and *D;* 9, *C* and *D;* and 10*B*).

CASE II. D.H., a three day old white male, was admitted to the hospital with an enlarged liver and spleen. A nodular mass was felt in the skin overlying the right scapula, and another smaller mass over the right anterior chest. The liver was enlarged 4 cm. and the spleen 5 cm. below the costal margin. On August 23, 1952 a biopsy of the left tibial marrow was not diagnostic, but a biopsy of the left scapular skin nodule revealed a very anaplastic tumor consistent with the diagnosis of a sympathicoblastoma. A primary site was never found. The patient was discharged from the hospital with no specific therapy and a grave prognosis.

He was seen in the clinic on September 5, 1952 at which time there were many more nodules present in the skin, involving the entire body, varying in size from several millimeters to a centimeter. The hepatomegaly and splenomegaly persisted. The patient was, however, eating well and gaining weight. He was next seen on October 24, 1952, at which time the skin nodules were decreasing in size and number. During the next four months all of the nodules disappeared, the liver and spleen returned to normal size, and the infant appeared healthy. He has had no further difficulty and is living and well at the present time.

DISCUSSION

The two year survival rate of 50 per cent indicates that neuroblastoma is not a hopeless disease. While neuroblastoma may rarely regress spontaneously, radiation therapy must significantly alter the ultimate course of the disease, since there was no instance of complete surgical removal of the tumor in our series. The tumor doses

FIG. 7. Case 1. (*A* and *B*) Roentgenograms of the abdomen, taken on December 1, 1953 prior to radiation therapy, demonstrate calcification anterior and to the right of the first lumbar vertebral body. Note also the slight scoliosis present. (*C* and *D*) Roentgenograms taken on September 15, 1959, six years after radiation therapy to the right upper abdomen (3,700 r central tissue dose), reveal residual calcification, increase in the scoliosis, irregularities of the vertebral bodies and right ilium, and narrowing of the T12–L1 interspace.

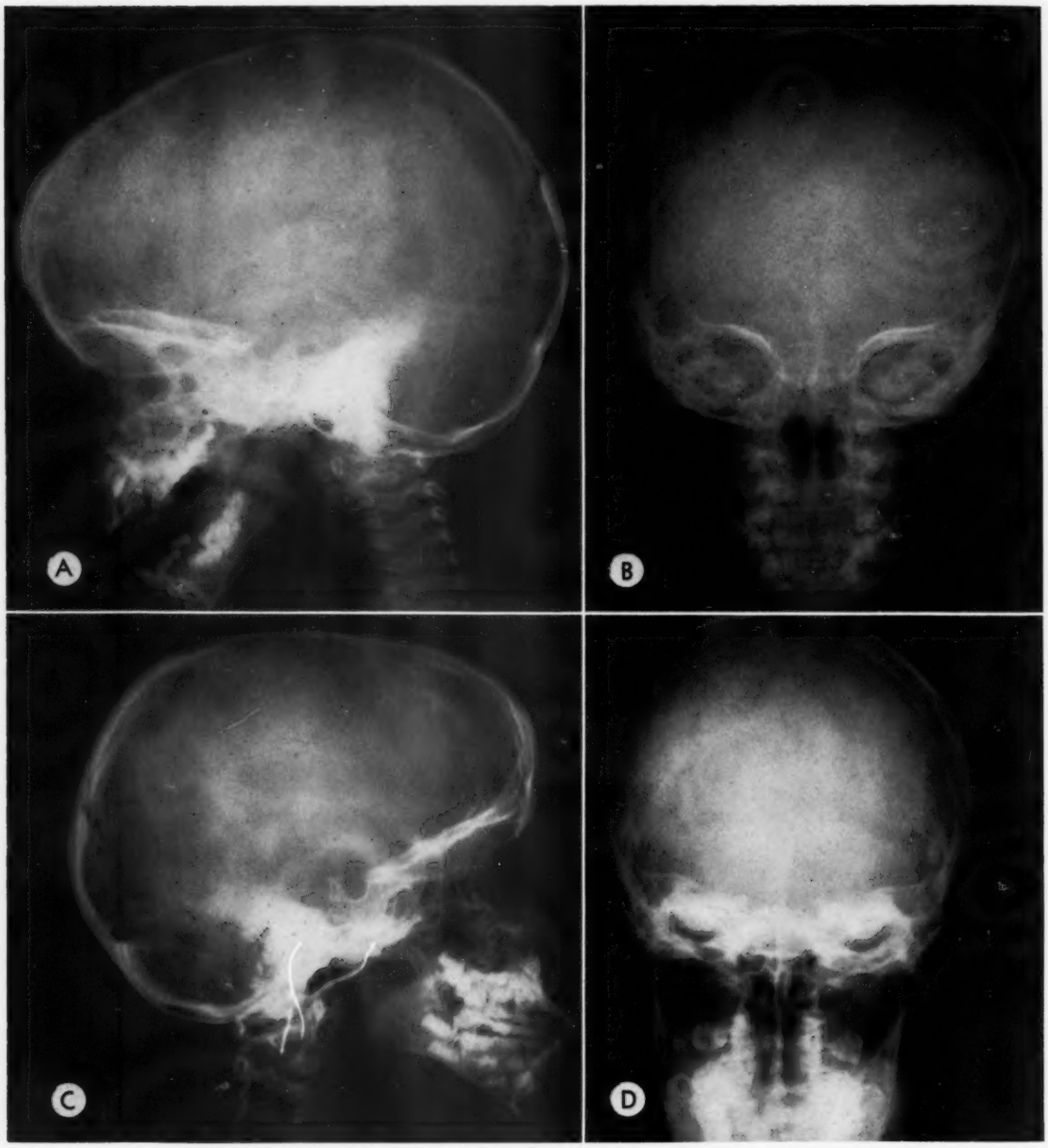

Fig. 8. Case 1. (*A* and *B*) Roentgenograms of the skull taken on January 29, 1954 reveal thickening and sclerotic changes in the right frontoparietal region. (*C* and *D*) Roentgenograms taken on September 15, 1959 demonstrate resolution of the bone abnormalities and the calvarium at this time appears normal (2,400 r air).

given covered a wide range (1,700 to 4,500 rad), and there was no correlation of dose with survivals. This may indicate that a specific predetermined dose is not as important as the response of the tumor to the radiation in each case.

It appears that the site of origin of the tumor may be the most important prognostic sign. No deaths have occurred in those patients with tumors originating in an extra-adrenal site. On the other hand, there is only 1 survivor in the group in which the primary site was the adrenal gland. We have no explanation for this

Fig. 9. Case 1. (*A* and *B*) Roentgenograms taken on February 27, 1954 demonstrate an osteolytic lesion with a sclerotic component in the proximal right tibia. Note the cortical expansion. (*C* and *D*) Roentgenograms taken on September 15, 1959 reveal the tibia to be normal.

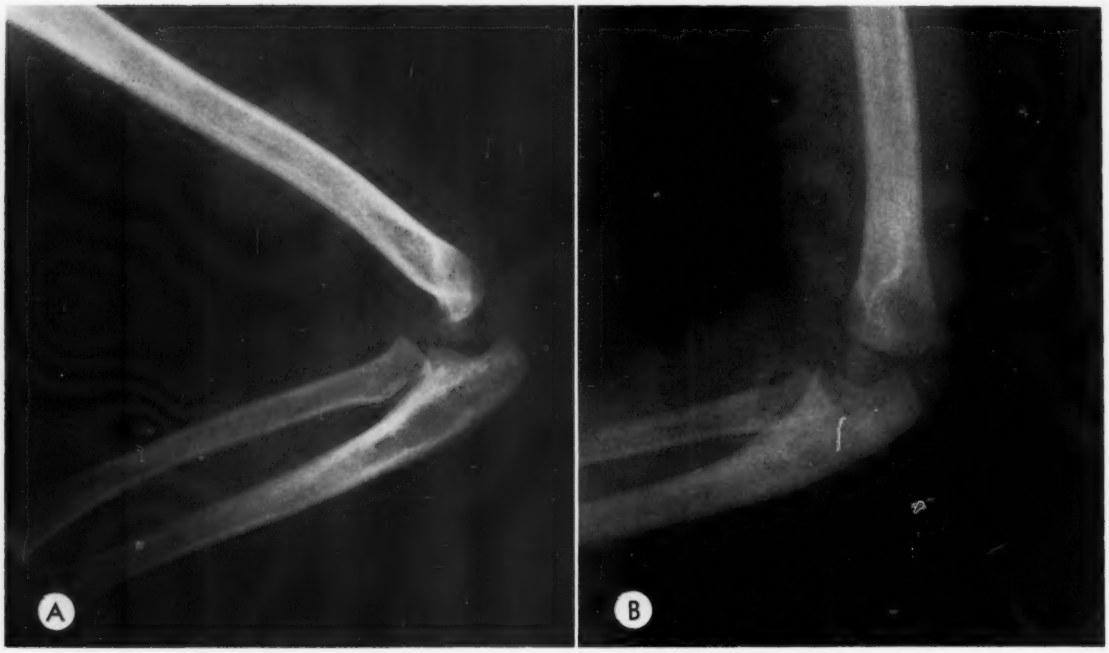

Fig. 10. Case 1. (*A*) Roentgenogram of the left elbow taken on January 20, 1955 demonstrates a metastatic lesion (biopsy proved) in the proximal portion of the ulna. (*B*) Follow-up roentgenogram taken on March 6, 1956 reveals marked interval improvement (1,200 r air).

apparent difference. Perhaps the adrenal lesions are more difficult to detect early, lying dormant and allowing more time for dissemination. Other factors may be differences in the vascular bed of the adrenal gland leading to early blood borne dissemination, or alterations in the host resistance to these tumors. Analysis of our data (Table IV) indicates that there is no apparent difference related to the ages of the patients. There is a tendency for the extra-adrenal lesions to be more mature, and ganglioneuroblastomas were more common in this group. It is evident, however, that the adrenal lesions metastasize more often, in contradistinction to extra-adrenal tumors. Thus it is conceivable that neuroblastomas originating in the adrenal gland are inherently different neoplasms with a more malignant behavior, even though no morphologic evidence for this exists. Dargeon[6] reports survival of 15 patients out of 108 with neuroblastomas. Of these 15 surviving patients, in only 1 did the lesion originate in the adrenal gland, again implying a better prognosis for extra-adrenal lesions.

Although generalizations concerning survival and the histologic pattern of the tumor cannot be made from this small series, our findings, and those reported by others, suggest that the survival is significantly better in the ganglioneuroblastoma group. [14,30] Assuming that these tumors arise by dysontogenesis of cells which possess maturational potential, a unique viewpoint for histopathologic evaluation is probably required. In typical adult-type

Table IV

Comparison of Adrenal and Extra-Adrenal Tumors

		Adrenal	Extra-Adrenal
Age	Under one year	3	4
	Over one year	7	9
Histology	Ganglioneuroblastoma	1	5
	Neuroblastoma	5	6
	Sympathicoblastoma	4	2
Metastases	Present at diagnosis	5	0
	Present later	3	2
	Number/total	8/10	2/13

neoplasms, *e.g.*, carcinoma of the breast, colon, etc., prognosis tends to be related to the most anaplastic or most undifferentiated foci of a given tumor. In dealing with dysontogenetic tumors, on the other hand, one should conversely look to the most differentiated area, which may reflect the capacity of the embryonal cells to mature. The evidence that regression of neuroblastoma is associated with cell maturation is somewhat limited.[5,11,22,25] This evidence is, none the less, well documented and relatively clear-cut, and would seem to justify this viewpoint.

The radiation therapy was given in a single course, in contradistinction to the two separate courses others have recommended.[35] The treatment plan has been to institute radiation therapy after the immediate effects of the surgical procedure have passed. Surgical intervention does not make irradiation an emergency procedure. If emergency radiation therapy is deemed important, then it would be preferable to initiate therapy preoperatively. Preoperative irradiation may be useful to render the tumor more accessible surgically and to reduce the growth potential of any remaining tumor tissue.

The expected sequelae of radiation therapy were observed in most cases, but in no instance did they present serious complications. In many patients, depression of the bone marrow occurred, but this was only temporary with no instance of permanent depression. This effect did alter the treatment plan in some of the patients so that the contemplated tumor dose was not achieved. No radiation nephritis or skin complications were noted.

There were 3 instances of radiation induced scoliosis. Two occurred after irradiation of the mediastinum: the first, a five month old girl who received 4,500 rad, and the second, a three year old girl who received 2,900 rad. Both patients are living and well after thirteen and ten years, respectively. The third patient was presented in detail above (Case 1). Neuhauser *et al.*[21] reported 34 children who received radiation to the spine, 3 developing scoliosis, and 21 having various bone changes demonstrated on roentgenograms. It has been recommended that the whole vertebral body be included in the treatment field so that wedging and resultant scoliosis will be less likely to occur. It is conceivable that tumor involvement of the vertebral body, muscle and nerves may contribute to the development of the scoliosis.

There were 3 instances of radiation induced osteochondroma. The first case was a five month old boy who had an osteochondroma of the left third rib removed five years after receiving 3,000 rad to the left upper chest for a mediastinal neuroblastoma. The second case was a fifteen month old boy who developed an osteochondroma of the left ilium and a moderately hypoplastic ilium after receiving a tumor dose of 1,750 rad to the left paralumbar region. The third case was a three year old girl who developed an osteochondroma of the iliac crest several years after receiving 2,100 rad to the left abdomen for a paralumbar sympathicoblastoma. Neuhauser *et al.*[21] report development of osteochondroma in 5 of 34 children receiving radiation therapy.

A therapeutic agent which we have found to be a useful adjunct in patients with disseminated bone disease is radioactive phosphorus, given either intravenously or orally, in weekly 1 mc doses. The dose used is often limited by the precarious condition of the bone marrow secondary to previous radiation therapy and disseminated disease This can be helpful in the relief of bone pain secondary to metastatic involvement. We have had no experience with the use of chemotherapeutic agents such as cortisone, antimetabolites, cytotoxins, or vitamin B 12.[3,9]

The 2 case presentations reveal the difficulty in predicting the course of the disease in children with neuroblastoma. The presence of skeletal metastases is considered a grave prognostic sign. Case 1 had several documented areas of bone involvement, yet she is living and well six years after the diagnosis. There are 6 similar cases reported in the literature of neuroblastoma with

skeletal metastases and survival.[1,7,10,12,28,32]

Case II illustrates the difficulty in evaluating the mode of therapy. This patient had only a biopsy of a skin nodule. with no definitive therapy, yet he is living and well eight years after diagnosis. This most likely is an example of spontaneous regression of the tumor secondary to differentiation or maturation of the elements of the tumor.

The steadily increasing survival rate during the past few decades seems to parallel the more intensive use of surgery and radiation therapy. We had no case in which the tumor could be extirpated completely at surgery, thus we can reasonably assume that the radiation destroyed the tumor or changed its biologic behavior. Even though a curative approach is not indicated when extensive metastases are present, radiation therapy affords excellent palliation. These factors, in addition to the unpredictable course of the disease, demand continued therapeutic efforts, since occasionally an unexpected long survival will result.

SUMMARY

A review of the course and therapy of 28 cases of neuroblastoma has been presented, with a two year survival of 50 per cent recorded in 26 patients. The treatment of choice is complete surgical removal of the tumor followed by radiation therapy to the tumor bed. Radiation therapy is useful for the treatment of metastatic disease.

Our data seem to indicate that the site of origin of the tumor may be the most important prognostic factor. In this series, only 1 patient out of 10 is surviving whose primary tumor was in the adrenal gland, while all patients with extra-adrenal primary sites have survived. In addition, the presence of metastases and the histologic characteristics of the tumor are of prognostic importance.

Two cases with metastatic disease and long term survival are presented.

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ADVANCES IN APPLICATIONS OF RADIOISOTOPES IN PEDIATRICS*

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AT THE present time it would seem that most diseases may be studied in some aspect by radioisotopes—a means which constitutes a significant advance over conventional clinical laboratory tests, since these generally indicate only the static level of a substance or a cell, whereas isotopic labeling makes it possible to measure the rate of formation and/or destruction, commonly called "turn-over rate," due to the fact that radioactive elements are not distinguished from their stable counterparts by the body. For this reason, it is possible to "label" the stable isotopes in the body with their radioactive nuclides or "tag" normal constituents of the body with radioactive isotopes. Examples are the use of a radioisotope of iodine to label the inert iodide in the body in order to measure the rate of its inclusion into an organic compound, or the tagging of hemoglobin in the red blood cell in order to estimate red blood cell mass, rate of mixing of labeled cells, or the rate of red blood cell destruction. C^{14} (radiocarbon) and H^3 (tritium) have been used with increasing frequency to tag organic compounds of biologic importance. There are no readily usable radioisotopes of oxygen or nitrogen.

In most cases tests with radioisotopes offer little risk to the patient from exposure to ionizing radiations. Some, such as red blood cell tagging with Cr^{51}, result in very little radiation exposure, actually only of the same order of magnitude as that received by the entire population from natural radiation, which has been estimated to be 0.095 rad yearly at sea level.[21] This increases significantly with altitude. A patient given a Cr^{51} diagnostic test receives about an additional 0.030 rad. Other tests using I^{131} or Fe^{59} result in more exposure, about 1 to 1.5 rad to the thyroid per μc I^{131} taken up and 0.2 rad to the hematopoietic system per μc of Fe^{59} retained. Doses of 10–50 μc are usually given in most clinical tests using I^{131}, I^{132}, and Fe^{59}. The radiation received is of the same order of magnitude as that received as a result of conventional roentgenographic examination.*

Instrumentation continues to improve and since the present author's[26] review in 1956, increased sensitivity in instruments has made possible a decrease in dosage of radioisotopes and, thus, in the possible hazards associated with radiation. In most other tests not mentioned above, a tracer dose of 0.5 to 10 μc is often sufficient. Among the new instruments are scintillators, which have a well-shaped sodium iodide crystal in which the sample to be counted is placed, with an efficiency approaching 50 per cent; liquid scintillation detectors, in which the specimen to be counted is dissolved in the scintillation solution with 5–10 per cent efficiency for H^3 and up to 50 per cent efficiency for C^{14}; and gamma-ray spectrometers which allow the differential detection of two or more radioisotopes in a single sample.

Scintillation scanning is now commonly done to reveal the isotope-rich areas of the body. The scanner has a scintillating crystal which is collimated to see various sized fields and is moved mechanically to scan the area desired. Typical scans of the thyroid are shown in Figures 1, 2 and 3. Scintillation scanning is useful in detecting

* The roentgen unit, r, refers to exposure. Diagnostic roentgenographic study of congenital heart disease delivers 140 or more r; chest fluoroscopy of infant, 15–20 r per minute; and chest roentgenograms 0.5 r. A rad, roentgen absorbed dose, is 1.04 r.

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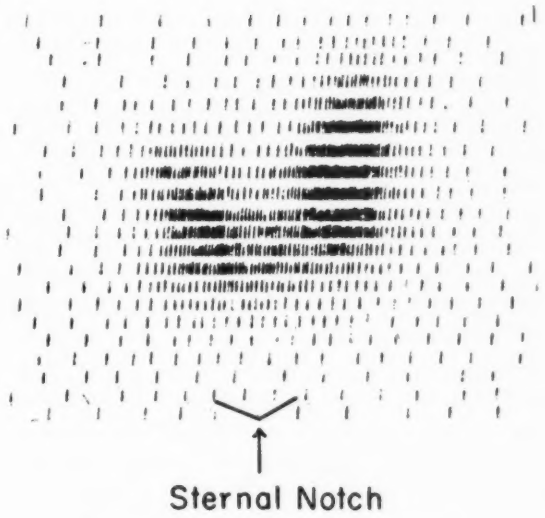

Fig. 1. Scintiscan of a normal thyroid.

"hot" (increased uptake of I^{131}) or "cold" (decreased uptake) nodules in the thyroid, cervical lymph nodes, or elsewhere in the body when activity of thyroid metastases is to be determined. "Hot" nodules are probably more common in the endemic areas of goiter, *i.e.*, the Great Lakes area of the United States. Nodules are less common in areas where the iodine intake is adequate.

The following is a discussion of the organ and system disturbances in which radioisotopes may be used in pediatrics.

DIAGNOSTIC APPLICATIONS

THYROID

A measure of thyroid function may be had by labeling the iodide pool of the patient with I^{131} or I^{132}. The latter reduces the radiation dose to the thyroid to about 1/25th of that received from I^{131}, but it must be milked from Te^{132} the day it is used because of the 2.26 hour half life.[11] Table 1 shows the range and the mean thyroid uptake which we find in normal as well as in several disturbed thyroid states.

Table I

PER CENT I^{131} UPTAKE IN THYROID 24 HOURS AFTER ORAL ADMINISTRATION

	Per Cent Range
Euthyroid	8–35
Hypothyroid	0– 7
Hyperthyroid	35–90
Simple Goiter	14–35
Goitrous Hypothyroid	44–87

Classic hypothyroidism in young children is difficult to diagnose if the deficiency is not marked. Blood protein bound iodine, cholesterol, and the basal metabolic rate tests are often unreliable. Even so, such tests should be made first and, if results are borderline or questionable, tests with radioiodine can be considered. Thyroid uptake of I^{131} is below normal (less than 8 per cent in 24 hours) with a low conversion ratio of the blood I^{131}. Athyreosis in infants is not always easily recognized, but I^{131} tests should not be performed immediately or routinely in order to avoid criticism as to the possible ill effects of radiation, even though the

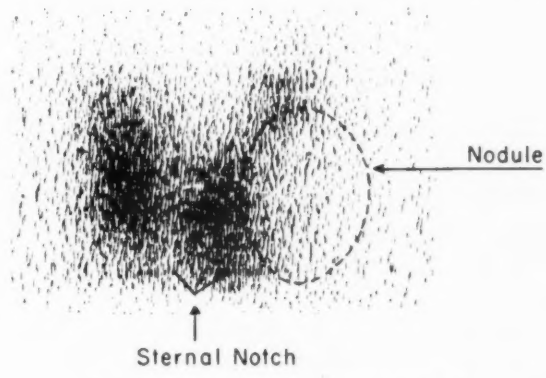

Fig. 2. Scintiscan of a "cold" nodule in a thyroid gland.

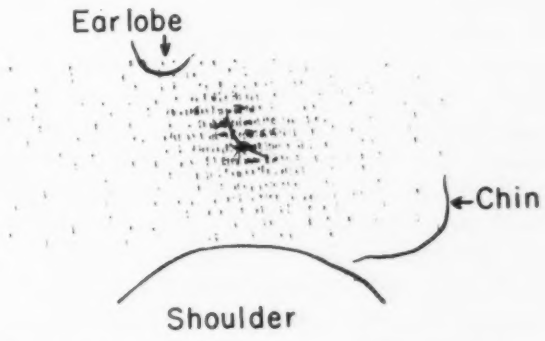

Fig. 3. Lateral scintiscan. Aberrant thyroid tissue at base of tongue. Normally situated tissue was not present.

amount of radiation to the infant's thyroid is low (30 to 50 rad).

Hyperthyroidism is uncommon in children in a florid form; forme fruste occurs more often, but not frequently. In cases where protein bound iodine, basal metabolic rate and blood cholesterol tests are borderline high normal, I^{131} uptake and conversion ratio are usually elevated and definitely helpful.

The writer has found previously unknown iodinated protein compounds in colloid goiter by using the resin adsorption test, radioautograms, and resin column separation, and has suggested that colloid goiter is another metabolic defect. In goitrous hypothyroidism, the thyroid uptake of I^{131} is increased. Due to a postulated inherited defect or to the lack of a specific enzyme or enzymes, three types of defects seem to exist: (1) inability of the gland to convert inorganic iodide into organic iodine compounds, (2) inability to couple iodotyrosines to form triiodothyronine and tetraiodothyronine (thyroxin), and (3) absence of the enzyme (deiodinase) which breaks down unused iodotyrosine radicals and so makes their iodine available for re-utilization as iodide. Probably other types of defects will be delineated by radioisotopic techniques in the not too distant future.

Determination of thyroid I^{131} uptake is not a full measure of function; the conversion of inorganic iodide to organically bound iodine (thyroxine) and its release may be a more thorough test of thyroid function.

At best, I^{131} tests of thyroid function are not a means of definitely detecting borderline states of hypothyroidism or hyperthyroidism, but they are helpful. It is better to assess the patient first by careful history, physical examination and routine laboratory tests; the I^{131} test can be performed if doubt persists.

Various conversion methods (ratio of organic to inorganic iodide) have been suggested since the report by Scott and Reilly[32] in 1954, who used an anionic resin to separate the I^{131} as iodide in plasma from that converted to protein bound I^{131}. The conversion ratio *per se* does not give as complete information as when the per cent of I^{131} converted to PBI^{131} is normalized to a standard I^{131} dose and body weight. Reilly *et al.*[27] found that the counts per second per cent converted by euthyroid adults was 4.1, 12.2 and 17.3 at 24, 48 and 72 hours after I^{131} dosage. In hyperthyroidism these values were 136, 216 and 198 at 24, 48 and 72 hours and 0, 2.5 and 1.2 respectively in hypothyroid patients. Higher values were obtained in euthyroid children. These were 6.1, 17 and 21 counts per second per cent for similar time periods. The PBI^{131} conversion showed far less overlap in the various thyroid states than did the gland uptakes. PBI^{131} conversion may be expressed as percentage of the dose administered per unit of plasma or blood with similar results.

A test of thyroid function has been developed using I^{131} labeled triiodothyronine which is incubated with a blood sample and the plasma binding determined differentially by measuring the amount of triiodothyronine which is not bound by plasma and which diffuses into the red blood cells.[14] The normal euthyroid range is 10–17 (%/100 hematocrit). Plasma from hypothyroids binds more because of low initial plasma levels which exist due to the paucity of thyroxine released to the plasma by such a thyroid gland, and all red cell uptakes range from 5 to 11. Conversely, hyperthyroidism results in increased uptakes in excess of 16 since the plasma is more nearly saturated from endogenous sources. This test is especially desirable for use in children since the patient receives no radiation exposure.

PARATHYROID

The parathyroid states of hyper- and hypoactivity have been studied with Ca^{45}, but its 164 day half life and the relatively weak beta emission make this isotope unsuitable for studies in children. Recently Ca^{47} has been made available; it has a 4.7 day half life and emits gamma rays which make it most useful in *in vivo* and *in vitro* studies involving calcium metabolism.[19]

PANCREAS

While studies with radioisotopes in diabetic children have not been recorded, it is possible that radioisotopes can be used safely and successfully. The extent of diabetes and the mysteries of its intermediary metabolic pathways are being determined with the use of isotopically-labeled (H^3 or C^{14}) glucose, adrenal steroids, and fats. Searle *et al.*[33] and others[35] have used C^{14} glucose in normal and diabetic patients to compare the action of insulin and tolbutamide on the glucose oxidation rate. This was found to be approximately 50–60 mg./kg. body weight/hr. in both normal and diabetic subjects. A glucose turnover rate of 54–150 mg./kg./hr. was observed in diabetics as compared to 72–98 mg./kg./hr. in normal patients. Searle and coworkers have come to the conclusion that tolbutamide potentiates the action of insulin.

LIVER

Brent and Geppert[3] evaluated infantile jaundice by using rose bengal I^{131}; they distinguished between intra- and extrahepatic causes. Blahd and Nordyke,[2] also using rose bengal I^{131}, employed a technique by which the blood is counted externally at the ear. The normal range of rose bengal retention is about 40 per cent in 20 minutes. Higher values are obtained in cases of chronic infectious hepatitis (48 per cent), congestive heart failure (61 per cent), cirrhosis with ascites (63 per cent), and cirrhosis with ascites and jaundice (75 per cent).[2] It is doubtful whether these radioisotopic tests would be justifiable or practical in pediatric practice.

DIGESTIVE TRACT

The malabsorption states (cystic fibrosis of the pancreas and steatorrhea) continue to be studied with promising results. Lavik *et al.*[18] have reported their work on protein digestion and absorption in children with and without cystic fibrosis of the pancreas. They administered orally 10 to 40 μc of I^{131} labeled human serum albumin and measured the I^{131} in blood and urine specimens. The normal blood I^{131} level after 2 hours is 16 per cent of the dose, with a range of 11 to 21 per cent. After 12 hours, 18 to 50 per cent of the I^{131} is found in the urine with a mean of about 18 per cent. Very little is found in feces. In pancreatic insufficiency, the 2 hour blood I^{131} level is much lower than normal, 1–2 per cent,[6] the 12 hour urine excretion is 5–18 per cent with a mean of about 10 per cent in 72 hours; 20 to 60 per cent is found in the feces.[7] Spector *et al.*[38] found that utilization of I^{131} labeled corn oil for the study of fat absorption in steatorrheas proved advantageous. Blood, stools, and urine were counted for I^{131} during a 48 hour period. Fat absorption was found to be lower and excretion higher in these conditions. The test also indicated the severity of these states.

The normal blood level of I^{131} for 4 hours after the administration of I^{131} labeled triolein is about 14 per cent with a range of 8–18 per cent. In carcinoma of the pancreas and pancreatitis, blood levels of 3 per cent and 7 per cent, respectively, were observed. When I^{131} oleic acid was administered, no significant change from the normal 4 hour level of 13 per cent was noted. This was depressed in steatorrhea.[30] In malabsorption states, the tests which can be performed successfully and safely in children are absorption of fats by I^{131} triolein or oleic acid and I^{131} albumin test for bowel digestion by trypsin. It is advisable to block the thyroid with Lugol's solution prior to the tests involving I^{131} labeled compounds in order to avoid unwanted radiation to the thyroid.

CIRCULATORY SYSTEM

Advances have been made in blood volume determinations with Cr^{51} tagged red blood cells; I^{131} HSA; in cases of vascular defects, such as arteriovenous shunts, with Na^{24}; and in peripheral absorption for diagnosis of circulatory defects and detection of septal defects with sodium 2,6-diiodosulfonilate tagged with I^{131}. There is an increased demand for blood volume determinations in cardiac patients with and without failure (congenital and acquired)

for routine as well as research testing and also in cases of nephrosis.

Cr^{51} RBC is probably the most reliable of the radioisotopic tests to estimate blood volume although such a determination is not a true one, for only the Cr^{51} RBC mass is measured. The total volume is then estimated by using the hematocrit value. I^{131} HSA is a plasma tag which may leave the blood stream during the test and result in a falsely high volume determination. Theoretically, a combined measurement by radioisotopes of both the RBC mass and plasma volume should approximate a true blood volume. The mean blood volume obtained with Cr^{51} was found to be 65.5 ± 5.9 cc. per kg. body weight with a range of 45 to 81 cc./kg.[12,29] It was found to be elevated in metastatic carcinoma,[28] right and left and right heart failure[29] and in secondary polycythemia. Plasma volumes in normal children were about 40 cc. per kg. These were obtained by using I^{131} HSA.[17]

Cardiac output has been measured using I^{131}, I^{131} HSA, Cr^{51}, and I^{131} rose bengal. The normal mean was observed to be 3.3 ± 0.8 l./min./m.^{2}.[15] Na^{24} has been used to measure pulmonary circulation time by placing a counter over the heart. The mean normal time was 5.4 seconds; it may be as high as 10 seconds in cases of pulmonary emphysema.[25] Na^{24} is also useful in determining the viability of skin grafts by measuring the biologic half life.* This is normally 9 to 20 minutes but it is longer in nonviable grafts.[1]

The detection of septal defects is an example of the helpful application of a radioisotope to a definite clinical diagnostic problem.

Sodium 2,6-diiodosulfonilate tagged with I^{131} has the following advantages: it can be synthesized easily; it is labeled in high specific activity; it has a very low toxicity; it is excreted very rapidly in the urine; its biologic half life is less than one hour; tests can be repeated frequently; it does not localize in the thyroid gland or other tissues; it is not a metabolite and, therefore, does not enter any "pools"; it emits gamma radiation and radiation exposure is reduced below that of Na^{24} and I^{131} HSA, which are often employed for dynamic studies. The procedure, briefly, is as follows: A well collimated scintillation crystal detector is placed over each side of the heart, connected to separate recorders, and approximately 3 μc of the compound is injected intravenously. The differentiation of entry of the radioisotope into each side of the heart is detected on the recorders by the time and height differences of the dual records.[22]

* The biologic half-life is an expression of the clearance rate of isotopes or compounds by a patient and is the time in seconds, hours, or days needed for the reduction of the initial concentration by one-half.

HEMATOPOIETIC SYSTEM

The following conditions have been studied more extensively in recent years: the hemolytic anemias (congenital and acquired), iron deficiency anemias, megaloblastic anemias, leukemias and secondary polycythemia. Fe^{59} has been employed in these conditions particularly to measure the rate and amount of iron turnover in plasma productions of red blood cells and hemoglobin red blood cell iron turnover and survival time. Cr^{51} is perhaps more usable than Fe^{59} for measuring red blood cell survival time. An ingenious and profitable study of the absorption of iron in infants and children employing Fe^{59} has been reported by Smith and Schulz.[36]

The diagnosis of pernicious-like (megaloblastic) anemia in childhood using the Shilling test may be made by orally administering about 0.5 μc of Co^{60} labeled vitamin B_{12} so that the excess B_{12}, both unlabeled and labeled, which is absorbed will be excreted in the urine. The normal excretion of Co^{60} in the 24 hour urine is usually 7–22 per cent.[3] In pernicious anemia it is less than 3 per cent because of lack of absorption from the gastrointestinal tract. A similar lack of absorption is observed in sprue, malabsorption syndrome[23] and in postgastrectomy patients.[3] Following the administration of the intrinsic factor an elevation in excretion of 2 to 8 times the original activity is encountered in per-

nicious anemia (3–30 per cent) and in post-gastrectomy anemia (3–18 per cent). Some elevation may be encountered in sprue and in the malabsorption syndrome.

Labeled cells may be used to study various anemias. The apparent half time of survival of red blood cells labeled with Cr^{51} ranges from 29–35 days; values lower than this may be observed in iron deficiency anemia (17 days), hemolytic anemia (1–7 days) and anemia of infection (17–22 days).[4]

Studies with Fe^{59} can reveal a great deal about the dynamics of the hematopoietic system. These are generally complex and fall more in the research category rather than in routine clinical testing. After incubating the patient's plasma with Fe^{59}, it is injected and its disappearance rate from the blood stream determined.[16] The normal mean half-time of loss from the blood is 1.75 hours. This is decreased to 30 minutes or less in iron deficiency anemia, polycythemia vera, hemolytic anemia, anemia of infection and pernicious anemia, and increased in aplastic anemia.[16] The plasma iron turnover rate may be calculated if the inert plasma iron is known. The normal range is 21 to 37 mg./da. In endogenous hemochromatosis, iron deficiency anemia, and anemia of infection, it rises to approximately 35 to 50 mg./da.[5,24] The hemoglobin formation rate may also be calculated from Fe^{59} studies. This has been found to be 0.835 per cent per day in normals and 0.943 per cent in endogenous hemochromatosis, and as high as 2.28 per cent per day in iron deficiency anemia.[24] Total hemoglobin formed can also be calculated. It is 5–8 gm. per day in the normal, 6.6 gm. per day in hemochromatosis and 9.9 gm. per day in iron deficiency anemia.[24] The labile iron pool was observed to be 90 mg. in normal patients and up to 187 mg. in endogenous hemochromatosis and down to 14 mg. in iron deficiency anemia.[24]

NERVOUS SYSTEM

Some of the less frequently used but helpful applications of radioisotopes in diagnosis of lesions of the nervous system are in conjunction with brain tumors: localization by I^{131} HSA, I^{131} diiodofluorescein, K^{42}, K^{43}, or P^{32} which is now used less often. The multiple measurements over the child's skull are too tedious for the yield and the results are not any more localizing than careful clinical and roentgenographic examinations.

OSSEOUS SYSTEM

Osteoporosis (Ca^{45}, P^{32}), refractory rickets (H^3), and osteosclerosis (Ca^{45}, Sr^{89}) have been investigated with considerable success by measuring blood levels and urinary excretion. In this manner radioisotopes have helped in decreasing the obscurity of absorption, turnover, and excretion of calcium and phosphorus.[4] Heretofore these studies have been impeded by the lack of suitable isotopes. The availability of Ca^{47}, Sr^{89} and Sr^{85}, all gamma emitters with suitable half lives, will aid in obtaining additional information with a minimum of radiation exposure to the subject.[40]

GENITOURINARY SYSTEM

Differential kidney function can be estimated with I^{131} tagged diodrast given intravenously and measured externally by a scintillation detector placed over each kidney, with the gamma radiation penetrating to the surface and into the crystal.[42]

I^{131} tetraiodophenolphthalein or I^{131} urokon probably could be used also. Glomerular excretion can be tested with C^{14} inulin, tubular excretion with I^{131} diodrast, and reabsorption with Na^{24} and H^3.

In studies of comparative renal function, both kidneys rapidly accumulate I^{131} labeled diodrast and, when normal, drop-off to about 43 per cent of the maximum peak in ½ minute and 31 per cent in 15 minutes occurs; inadequate function by either kidney may be measured by comparing the peaks. In complete ureteral obstruction, the retention curve rises to about 50 per cent of the normal value during the first few minutes,[42] and in a nonfunctioning kidney, the curve rises to about 35 per cent of the normal value, falling lower than normal in 15 minutes.[42]

BODY COMPOSITION

The fluid and electrolyte systems have been studied in instances of hypo- and hyper-states of natremia, kaliemia, chloremia, as well as edema, acidosis, alkalosis, dehydration, and diarrhea with the use of Na^{24}, K^{42}, and H^3_2O (tritiated water), Br^{82}, and S^{35} (compounds for studies on anions such as chloride).

The total body water using H^3 was found to range from 78 to 81 per cent with a mean of 79.3 per cent. This rose to 88.2 per cent in severe respiratory insufficiency.[37] The anion space or volume using Br^{82} was determined to be 27.5 ± 2.4 per cent of the body weight.[20] The total exchangeable sodium using Na^{24} or the longer lived Na^{22} was observed to be 39.5 ± 3.4 mEq./kg. and that of potassium using K^{42} and K^{43} to be 48.0 ± 4.4 mEq./kg. body weight.[20] It is possible to prepare extremely pure carrier free $K^{42,43}$ by alpha particle bombardment of argon gas using a cyclotron.

The procedures used by McMurrey and his colleagues[20] on adults might prove of value in pediatric investigations. These are recommended for instruction on methodology for use of radiosiotopes (the dilution principle) and for compositional data derived by calculation in basic science studies.[20]

THERAPEUTIC APPLICATIONS

Unfortunately, few advances have been made in the therapeutic application of radioisotopes. P^{32} for leukemia has been partly replaced by newly synthesized chemicals; however, it has proved very effective and remains the most definite radioisotope in children.

Strontium (Sr^{90}) applicators (beta radiation) for lesions of the cornea and conjunctiva are contraindicated. Cataracts, though rare, have been reported years after their injudicious use.

There is a somewhat promising advance being made with boron 10 compounds which, when intravenously administered, may localize in brain tumors. When the area is exposed to slow neutron bombardment from an atomic pile, the B^{10} captures the neutrons and subsequently releases alpha particles which expend all of their energy in the tumor and thus radiation damage to normal tissue is avoided.[10]

Crile[8] states that treatment of hyperthyroidism in childhood with I^{131}, because operative and medical management has been followed by hypothyroidism, is much simpler and probably safer than subtotal thyroidectomy or medical therapy. Surgical therapy of 21 cases resulted in such complications as recurrence (5 cases), hypothyroidism (4 cases), tracheotomy for postoperative edema and cord paralysis and keloids. I^{131} in small doses (4–5 mc) has been used by him during the past 10 years. Out of 22 cases, in 10 there were no ill effects, there was one recurrence, and 3 (14 per cent) became hypothyroid. De Gowin *et al.*[9] in a period of 10 years have given I^{131} therapeutically for hyperthyroidism to 10 children, carefully selected because of possible risks with medical and surgical therapy. They believe that I^{131} has a definite place in the teatment of hyperthyroid children. Other investigators who have followed similar groups of carefully chosen children appear to be in agreement.

Fewer recurrences and complications follow adequate operation of exophthalmic hyperthyroidism, and the writer prefers this to other therapy. Forme fruste can be controlled by proper medical management (propylthiouracil particularly). Though children with Graves' disease have been treated successfully with I^{131} therapy by the writer and others, Sheline *et al.*[34] noted the complication of adenomata with neoplastic possibilities in several children. At present, the writer does not recommend I^{131} therapy for children with Graves' disease because of potential genetic defects in their offspring and possible malignancy.[34] Though the dose to the gonads is no greater than that from diagnostic roentgenography of the spine and pelvis, this treatment should be the province of experienced investigators.

Metastases of thyroid cancer which have function (active) are very rare before the thyroid gland has been removed. However, such occur occasionally after thyroidec-

tomy, and I^{131} therapy can be tried. It can be given also to eradicate cancer in the thyroid gland if it recurs after thyroidectomy and further removal is not technically possible (adherence to trachea, vagus nerve, etc.).

Hahn[13] devised silver coated Au^{198} in colloid form for instillation into serous cavities which contain a malignancy. The inorganic silver favors the trapping of the colloid by the lymphatic vessels and the lymph nodes, and the Au^{198} irradiates the malignant cells. Such therapy is indicated in children with rare bronchogenic or pleural tumors which cannot be treated effectively otherwise.

SUMMARY

There are many clinical problems which can be solved, at least partially, by the judicious employment of radioisotopically labeled compounds, elements, vitamins, etc. A brief discussion of some of the actual and possible uses of radioisotopes in pediatric practice is presented.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

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Forty-third Annual Meeting: Broadmoor Hotel, Colorado Springs, Colo., May 10–14, 1961.

* *Ex officio.*

EDITORIAL

VESICOURETERAL REFLUX

In recent years, with general acceptance of the hypothesis that vesicoureteral reflux is never "physiologic" but always pathologic, considerable attention has been directed to establishing the diagnosis of this condition. Since it is not readily accessible to endoscopic evaluation, its discovery has depended until now on roentgenologic techniques. Initially, as in any field, these were rather crude and of a static nature. The retrograde passage of urine from the bladder to the kidneys, however, is a "reverse" type of phenomenon of a pathophysiologic nature, and more refined methods were needed which would also encompass the dimension of "time." The now apparent fact that reflux may be unilaterally or bilaterally intermittent, readily discernible one week but absent the next, has underscored the dynamic nature of this phenomenon. These disturbing vagaries were thought to be inherent in the process, but it is now recognized that they are partially the result of imprecise application of our investigative methods. The situation, which may be compared to the description of an elephant by six blind men in the old Hindu fable, may be justified by the tendency frequently observed in medicine to assay the clinical picture by momentary symptomatology.

Thus, for some time, patients, particularly children, presenting pyrexia with recurrent pyuria, pyelonephritis, abdominal pain, and enuresis have been discovered to have vesicoureteral reflux, either primarily or secondarily, as a cause of their symptoms. It is not unusual to find that such patients are treated strictly from a "medical" standpoint, unless the manifestations are quite severe. The apparently favorable response obtained from instituting appropriate antibiotic therapy, coupled with a regimen of frequent and multiple voidings, seems to support the correctness of the procedure. A feeling of security is also engendered by the knowledge that the phenomenon is rarely seen in adults except with neurogenic bladder disorders.

Recently, Hodson and Edwards,[1] in an excellent article, have drawn attention to a possible link between the phenomenon of vesicoureteral reflux and chronic pyelonephritis, seen not only in childhood but also in the adult. They reported 10 personal cases in which vesicoureteral reflux was encountered in an unexpected manner and an additional 10 cases collected from the literature. On the basis of roentgenologic findings they classified these into 4 broad categories: (a) children with recurrent urinary infection; (b) young adults with clinical and roentgenologic signs of chronic pyelonephritis; (c) cases of unexplained renal osteodystrophy and uremia, and (d) cases showing roentgenologic evidence of chronic pyelonephritis in which the clinical findings are atypical.

This frequent association of vesicoureteral reflux and chronic pyelonephritis represents an additional reason, to several others, for an early recognition of vesicoureteral reflux by establishing an *a priori* diagnosis leading to a more aggressive approach to therapy, especially since later complications may cause death from renal failure.

The radiologic methods which are used at the present time in an attempt to demonstrate the presence of vesicoureteral re-

[1] Hodson C. J., and Edwards, D. Chronic pyelonephritis and vesico-ureteric reflux. *Clin. Radiology*, Oct., 1960, *11*, 219–231.

flux may be placed in two groups: the roentgenologic and the radioisotope methods.

The roentgenologic methods comprise intravenous pyelography, delayed cystography, voiding cystography and, occasionally, ascending lipiodol study. Hodson and Edwards consider voiding cystography as being the most practical and informative. They recommend that this method be carried out whenever the following findings are encountered on routine intravenous pyelography: (1) evidence of chronic pyelonephritis, (2) very small kidneys with generalized caliectasis, (3) unexplained nonobstructive dilatation of the upper urinary tract, (4) undue distensibility of the urinary tract, (5) bladder residue in a child, and (6) unexplained renal osteodystrophy. If image amplification equipment is available, cinefluorography may be utilized for performing voiding cystography; it has the obvious advantage of adding the element of motion to the static study, with a relatively low radiation exposure.

The radioisotope method was introduced in 1959 by Winter,[2] and an exhibit on its correlation with roentgenographic methods was presented at the Sixty-first Annual Meeting of the American Roentgen Ray Society in Atlantic City, September 27–30, 1960 by Krabbenhoft, Cobb, Gordon and Corbett.[3] Its advantages are several: namely, (1) lower radiation exposure, (2) detection of a definite number of cases previously felt to be negative when the above methods were used, and (3) continuous observation throughout the study which may be conducted as long as thought necessary. An inherent shortcoming is its failure to demonstrate reflux limited to the lower ureters. This would, of course, be indiscernible from the high background radiation from the bladder incident to its distention with the radioactive solution. Additional parallel studies comparing the isotope technique with the other methods should continue to assess the reliability of this technique. The low levels of radiation exposure would seem especially important in cases requiring follow-up study, particularly in the postoperative periods.

The surgical approaches to treatment of vesicoureteral reflux have been of paramount importance to urologists, largely in the last decade. They range from correction of any obvious bladder outlet obstructions to a direct attack on the ureterovesical junction in the more severe cases. They run the gamut from urethral dilatations to resection of urethral valves and sclerotic vesical necks. An attack on the vesical neck may be by the transurethral route or by performing a V-Y plasty, using a retropubic abdominal-type approach. A modified Hutch procedure may be employed on the ureterovesical junction, or ureteral reimplantation as advocated by Leadbetter may be preferred.

The manifold character of these procedures amply illustrates the lack of a satisfactory understanding of this problem. The assessment of the results obtained by them rests in no small part with the radiologist. It is important, therefore, that he be familiar with all methods with might help him to properly achieve the aim of early, accurate diagnosis and later evaluation of treatment methods.

Joseph O. Reed, Jr., M.D.

Children's Hospital of Michigan
Detroit, Michigan

[2] Winter, C. C. A new test for vesicoureteral reflux: An external technique using radioisotopes. *J. Urol.*, 1959, *81*, 105–111.

[3] Krabbenhoft, K. L., Cobb, J., Gordon, M., and Corbett, D. Vesicoureteral reflux: Correlation of roentgenographic and radioisotope methods. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., Nov., 1960, *84*, 977.

NEWS ITEMS

GOLD MEDALS AWARDED BY THE AMERICAN COLLEGE OF RADIOLOGY

At the Convocation ceremonies of the Annual Meeting of the American College of Radiology held at the Drake Hotel in Chicago on February 8–11, 1961, two Gold Medals, the highest award of the College,

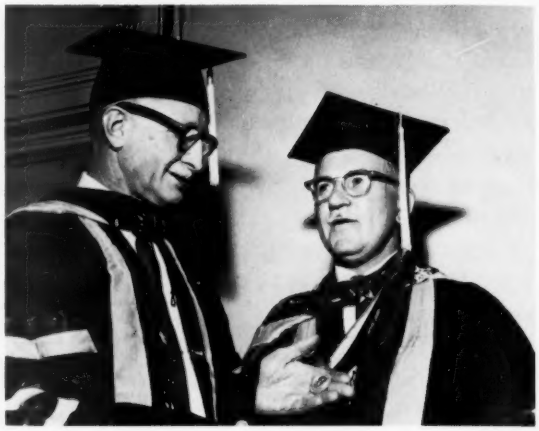
Dr. Vincent W. Archer (right) receives congratulations from Dr. Earl E. Barth (left), following academic ceremony in which Dr. Archer received the Gold Medal of the College of Radiology.

were presented by Dr. Earl E. Barth, President of the College.

Dr. Vincent W. Archer, radiologist from Charlottesville, Virginia, and Dr. Leo G. Rigler, radiologist from Los Angeles, California, were the recipients of the awards "for distinguished and extraordinary service to the College and to the profession for which it stands."

OFFICERS OF THE AMERICAN COLLEGE OF RADIOLOGY

At the Annual Meeting of the American College of Radiology held at the Drake Hotel in Chicago, Illinois, on February 8–11, 1961, the following officers were elected: President, Dr. L. Henry Garland, San Francisco, California; Vice President, Dr.



Dr. Leo G. Rigler (right) being congratulated by Dr. Earl E. Barth (left) for his award of the College's Gold Medal.

Philip J. Hodes, Philadelphia, Pennsylvania; Secretary-Treasurer, Dr. Fay H. Squire, Chicago, Illinois (re-elected); Chairman, Board of Chancellors, Dr. Theodore J. Wachowski, Wheaton, Illinois. Dr. Wallace D. Buchanan, South Bend, Indiana, and Dr. J. Maxey Dell, Jr., Gainesville, Florida, were elected to the Board of Chancellors.

The Executive Director of the American College of Radiology is William C. Stronach, 20 North Wacker Drive, Chicago 6, Illinois, and the Director of Public Relations is Hugh M. Jones, Chicago, Illinois.

The next Annual Meeting of the College will be at the Roosevelt Hotel, New York, New York, February 7–10, 1962.

CANADIAN ASSOCIATION OF RADIOLOGISTS

At the 24th Annual Meeting on January 22–25, 1961 of the Canadian Association of Radiologists held in Saint John, N. B., the following officers were elected: President, Dr. Donald L. McRae, Montreal; Vice President, Dr. Guillaume Gill, Montreal; Honorary Secretary-Treasurer, Dr. Robert G. Fraser, Montreal; and Associate Honor-

ary Secretary-Treasurer, Dr. Jean-Louis Leger, Montreal.

Dr. Edward B. D. Neuhauser of Boston, Massachusetts, was elected to Honorary Membership in the Association prior to his presentation of the 1961 Gordon E. Richards Memorial Lecture. Dr. Neuhauser is Radiologist-in-Chief of The Children's Hospital Medical Center in Boston and Clinical Professor of Radiology, Harvard Medical School.

The 1962 Annual Meeting will be held in Winnipeg, with scientific sessions beginning January 22 and continuing through January 24, at the Marlborough Hotel.

INTER-AMERICAN CONGRESS OF RADIOLOGY

The American College of Radiology, the American Roentgen Ray Society, the Radiological Society of North America, the American Radium Society, and the Section of Radiology of the American Medical Association have appointed their representatives to form an American delegation to the 7th Inter-American Congress of Radiology to be held in São Paulo, Brazil, September 3–10, 1961.

The following are the members of the American delegation appointed for these societies: Eugene P. Pendergrass, M.D., Chairman, Thomas Bond, M.D., Lois C. Collins, M.D., J. A. del Regato, M.D., Philip J. Hodes, M.D., Jesshill Love, M.D., and Wendell Scott, M.D.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE

The American Association of Physicists in Medicine adopted its first formal constitution and elected its first set of permanent officers under the new structure at the Annual Meeting in Cincinnati, Ohio, in December.

The constitution opens membership only to individuals who are primarily and professionally engaged in the application of physics to medicine and biology in medical installations, research or educational institutions. The objectives of the Association are to encourage interest and training in medical physics and related fields, to prepare and disseminate technical information in medical physics and related fields, to secure and maintain high professional standards for physicists in medicine and biology and to serve and represent their professional interests.

There are 132 charter members of the Association. Officers elected by its Board of Directors for 1961 are Warren K. Sinclair, Argonne National Laboratory, President; John Hale, University of Pennsylvania Hospital, Vice President; Charles S. Simons, University of Michigan Hospital, Secretary-Treasurer.

Inquiries about membership and activities of the Association may be directed to Dr. Simons at the Radiation Therapy Center, Ann Arbor, Michigan.

COURSE IN RADIOLOGICAL PHYSICS

A one year course in radiological physics, leading to the degree of Master of Science, is offered under the auspices of the Department of Radiology of the College of Physicians and Surgeons of Columbia University. It is designed to prepare candidates to carry out all the functions of a physicist in a hospital department of radiology; it would also furnish a foundation for those who wish to engage in research or applications in radiologic physics, radiation protection, and dosimetry. The course includes lectures, seminars, conferences, and laboratory work. Topics included are elementary and advanced radiologic physics, electronics, radiation standardization and protection, radioactive isotopes, biostatistics, radiobiology, instrument design, and clinical applications of radiation physics. Prerequisite for admission is a bachelor's degree with a major or strong minor in physics, or equivalent scholastic background, and a good academic record. A knowledge of general chemistry and general biology is very desirable.

As part of its national program for the training of radiological health specialists,

the Division of Radiological Health, Public Health Service, has awarded a grant to the University enabling financial assistance to qualified candidates. This aid will be in the form of tuition waiver as well as monthly stipend allowances. Applicants must be citizens of the United States or have filed a Declaration of Intent. Preference will be given to candidates who are sponsored by public health agencies for work in their area of responsibility or in closely related fields.

Inquiries should be addressed to Dr. H. H. Rossi, 630 W. 168th Street, New York 32, New York.

OHIO STATE RADIOLOGICAL SOCIETY

The Annual Meeting of the Ohio State Radiological Society will be held at the Deshler-Hilton Hotel in Columbus, Ohio, on May 19–21, 1961. A very interesting program has been arranged. Please write to Dr. Paul D. Meyer, 125 S. Grant Avenue, Columbus, Ohio, for further details.

REGISTRATION FOR THE SEVENTH INTER-AMERICAN CONGRESS OF RADIOLOGY

The Seventh Inter-American Congress of Radiology will be held in São Paulo, Brazil, September 3 to 10, 1961 in connection with the Eighth Brazilian Radiological Congress.

Registration applications and brochures concerning the Congress may be obtained by writing the Secretary General, Dr. Walter Bonfim Pontes, Rua Marconi n.° 94, 2.° and São Paulo, Brazil.

Registration fees:

I—For registration until May 31, 1961:

(a) Effective members	$35.00
(b) Accompanying members	$25.00
(c) Associate members	$30.00

II—After May 31, 1961:

(a) Effective members	$50.00
(b) Accompanying members	$40.00
(c) Associate members	$45.00

Registrations may be received until July 31, 1961.

Members: All members of Societies or Associations of Radiology and Nuclear Medicine of the Continent and those invited from other regions may participate in the Congress. Besides physicians, physicists, biologists, engineers, etc., recommended by a Society or Radiological Association of their country, are invited to submit their registrations.

Categories of members: (a) Effective members: Members of the Radiological Societies or Associations presented by the Counsellor of the Inter-American College or Brazilian College of Radiology. They have the privilege to share in the scientific and social activities, exhibitions and publications of the Congress. (b) Accompanying members: Family members are cordially invited to take part in the social activities of the Congress. Applications should be made in their behalf. (c) Associate members: Other specialists, physicists, engineers, and technicians, etc., presented by the Societies or Associations of Radiology with approval of the Counsellor of their Country, may share in the Scientific and social activities of the Congress.

JOSEPH AND SAMUEL FREEDMAN LECTURES

On Saturday and Sunday, April 22 and April 23, 1961, Dr. Harry Z. Mellins, Professor and Chairman, Department of Radiology, State University of New York Downstate Medical Center, will deliver the thirteenth annual Joseph and Samuel Freedman Lectures in Diagnostic Radiology at the University of Cincinnati College of Medicine. Radiologists desiring to attend are requested to write Dr. Benjamin Felson, Department of Radiology, Cincinnati General Hospital, for further details.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

ROENTGEN EXAMINATIONS IN ACUTE ABDOMINAL DISEASES. Second edition. By J. Frimann-Dahl, M.D., Ph.D., Chief of the Roentgen Department, Ullevål Hospital, Oslo, Norway. Cloth. Price, $15.50. Pp. 518, with 446 illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Ave., Springfield, Ill., 1960.

The first edition of this book in 1951 was an accumulation of useful information concerning the detection by roentgenologic methods of diseases which produce acute abdominal symptoms. Throughout is shown the author's knowledge of abdominal anatomy and physiology, and his extensive clinical experience and careful observation. The new edition is approximately two-fifths larger and is even more extensively illustrated.

The introduction deals with technical procedures, the methods of handling the acutely ill patient, and evidence of disease to look for when the roentgenogram is examined. The author mentions the use of high voltage roentgen rays and heavy filtration to reduce body dose but, correctly, he emphasizes the importance of an adequate examination because of the immediate threat to the patient's life inherent in many acute abdominal conditions. The first three chapters should be required reading as an introduction to diagnostic radiology, not only for beginners in this specialty but also for surgical trainees. The remaining chapters offer valuable information of use to all radiologists dealing with the specific conditions discussed therein. Even one carefully described case may teach an important lesson.

The book is profusely illustrated and the reproductions are good. In many places information is conveniently summarized in the form of diagrams. The effect of trauma on abdominal organs and other structures is reviewed.

This book is a worthy successor to the first edition and will continue to be a valuable source of information for many years.

ROSS GOLDEN, M.D.

TUMORS OF CHILDHOOD; A CLINICAL TREATISE. By Harold W. Dargeon, M.D., Attending Pediatrician and Chief, Pediatric Service, Memorial Hospital for Cancer and Allied Diseases; Attending Pediatrician, St. Luke's Hospital; and Associate Professor of Clinical Pediatrics, Cornell University Medical College, New York. Cloth. Price, $20.00. Pp. 476, with numerous illustrations. Paul B. Hoeber, Inc., 49 East 33rd St., New York 16, N. Y., 1960.

This book, subtitled "A Clinical Treatise," is divided into two parts with the first devoted to general considerations and the second to specific tumors. The author, chief of the pediatric service at Memorial Hospital for Cancer and Allied Diseases, has long been known to pediatricians because of his interest in and devotion to the problems of his clinical field as they apply to the younger age groups. His book, long awaited by those who have felt the need of an authoritative text in this area, is, to this reviewer, a bit of a disappointment. After reading it one is left with the impression that it is too long and diffuse to be an intimate summary of the author's beliefs, yet much too incomplete to be the definitive reference in childhood oncology.

While the dust jacket refers to experience with more than 6,000 children seen at Memorial Hospital, most of the data presented appear to be based on roughly 3,300 cases, almost equally divided between malignant and benign, collected from Memorial Hospital and the tumor registry over a thirty year period which terminated in 1956. This cutoff date would also seem to represent completion of the manuscript, since there are few references to work published during the past four or five years.

It is stated that this book is intended for the clinician and, from the age group with which it deals, it is primarily for the pediatrician. He will definitely profit from a reading of the first section where the author speaks, with the authority his position commands, on the general philosophy of therapy and patient care. One might take exception to some of the views, such as a routine rectal examination at three months of age and thereafter each six months until age four—the thought might be good but

the reviewer personally would be happy could he be assured that a careful palpation of the abdomen was done at these intervals. Later, another surprise, "Women with known cancer should be made aware that the fetus may become diseased if the primary tumor metastasizes to the placenta or involves it directly from the uterine wall,"—it might seem that bearing the burden of active cancer and pregnancy was a sufficient load without this bit of extraneous information.

In the second part of the book, covering specific tumors, the sections on cancer of bone, the neuroblastoma group, and the leukemia-lymphoblastoma family are quite useful and complete but in other areas, where frequent questions arise in pediatric practice, the text is inadequate for a reasonably trained specialist. It is impossible, for instance, to obtain a concise impression of how the physician might proceed to study an enlargement of the thyroid or parotid gland, or where he would start when confronted with sexual or somatic precocity at any age. Brain tumors are dealt with in some ten pages (including tables and charts), while spinal cord tumors are allotted less than three pages and the fascinating problem of functioning adrenal tumors is discussed in two pages.

The illustrations are generally good and in some chapters, such as the one on bone tumors, the reproduction of roentgenograms which are well chosen is excellent.

Paul V. Woolley, Jr., M.D.

Annual Review of Medicine. Volume 11. Edited by David A. Rytand, Stanford University School of Medicine; and William P. Creger, Stanford University School of Medicine. Cloth. Price, $7.00. Pp. 453. Annual Reviews, Inc., 231 Grant Ave., Palo Alto, Calif., 1960.

The latest volume in this excellent series of reviews presents 23 concentrated discussions on major medical topics. The subject matter has been wisely selected and the essays, though brief, show careful, critical preparation and editing.

These reviews, by pointing up the important and the useful, should be helpful to the physician who wants to keep abreast of the developments in medicine.

William S. Reveno, M.D.

X-Ray Technology. Second edition. By Charles A. Jacobi, B.Sc., R.T.(A.R.X.T.), M.T.(A.S.C.P.), Chairman, Medical X-Ray Technology, Oregon Technical Institute, Oretech Branch, Klamath Falls, Oregon; Chairman, Education Committee, Oregon Society of X-Ray Technicians; Chairman, Education Committee, Northwest Conference of X-Ray Technicians; formerly, Chief X-Ray and Medical Technologist, Medical Services Division, Atomic Energy Commission, National Reactor Testing Station, Idaho Falls, Idaho; and Donald E. Hagen, R.T.(A.R.X.T.), Technical Supervisor for C. Todd Jessell, M.D., and George R.Satterwhite, M.D., Radiologists, Portland, Oregon; formerly, Instructor, Medical X-Ray Technology, Oregon Technical Institute, Oretech Branch, Klamath Falls, Oregon. Cloth. Price, $10.00. Pp. 452, with 320 illustrations. C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3, Mo., 1960.

This book has been written primarily as a basic text for use by x-ray technicians who are beginning their training. The early chapters are devoted to a discussion of the fundamental physical concepts of roentgen-ray production and use. The ethical considerations of the technician's role and his responsibilities in radiation protection are well presented.

The body of the text is concerned with a systematic review of the human anatomy and the various techniques for roentgenographically examining each part. This is well illustrated with photographs of the standard positions and corresponding roentgenograms. Information regarding the use of cones, the Bucky diaphragm, necessary positioning devices, film size and exposure technique is included for each area to be studied. The value of the chapters on gastrointestinal and other special examinations is enhanced by instructions regarding patient preparation, general conduct of the examination and duties of the technician during each procedure.

This book is recommended as a basic text for technicians who are in the early stages of their career. It can also serve as a reference source for those who have mastered the fundamentals.

David Morse, Jr., M.D.

BOOKS RECEIVED

Congenital Malformations of the Heart. Volume II: Specific Malformations. Second edition. By Helen B. Taussig, M.D., Professor of Pediatrics, Johns Hopkins University School of Medicine; Physician-in-Charge, Cardiac Clinic, Harriet Lane Home, Johns Hopkins Hospital. Cloth. Price, $17.50. Pp. 1049, with numerous illustrations. Published for The Commonwealth Fund by the Harvard University Press, Cambridge 38, Mass., 1960.

Clinical Use of Radioisotopes; A Manual of Technique. Second edition. Edited by Theodore Fields, M.S., F.A.C.R. (Assoc.), Chief, Physics Section, Radioisotope Service, Veterans Administration Hospital, Hines, Illinois; Instructor in Radiology, Northwestern University Medical School; Attending Physicist, Cook County Hospital, Chicago, Illinois; Certified Medical Nuclear Physicist, American Board of Radiology; and Lindon Seed, M.D., Clinical Associate Professor of Surgery, University of Illinois College of Medicine; Director of Isotope Laboratories, Augustana Hospital, Chicago, Illinois, and Oak Park Hospital, Oak Park, Illinois; Consultant in Radioisotopes, Veterans Administration Hospital, Hines, Illinois. Cloth. Price, $10.50. Pp. 475, with 77 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, Ill., 1961.

Radiation Protection and Dentistry. The Postgraduate Dental Lecture Series. By Arthur H. Wuehrmann, D.M.D., University of Alabama School of Dentistry, Birmingham, Alabama. Cloth. Price, $6.50. Pp. 238, with 48 illustrations. C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3, Mo., 1960.

Safe Handling of Radioisotopes; Health Physics Addendum. Safety Series No. 2. By G. J. Appleton of the United Kingdom Atomic Energy Authority; and P.N. Krishnamoorthy of the Atomic Energy Establishment at Trombay, India. Paper. Price, $1.50. Pp. 120. International Atomic Energy Agency, Kärntner Ring, Vienna 1, Austria, 1960. Distributed in the United States and Canada by the National Agency of International Publications, Inc., 801 Third Ave., New York 22, N. Y.

Safe Handling of Radioisotopes; Medical Addendum. Safety Series No. 3. By Dr. F. Herčík of the Czechoslovakian Academy of Sciences; and Dr. H. Jammet of the Nuclear Research Center at Saclay. Paper. Price, $1.50. Pp. 80. International Atomic Energy Agency, Kärntner Ring, Vienna 1, Austria, 1960. Distributed in the United States and Canada by the National Agency of International Publications, Inc., 801 Third Ave., New York 22, N. Y.

Simultaneous Biligraphy; Technic and Interpretation; A Refresher Course. By Oscar M. Weaver, Jr., M.D., D.A.B.R., Stevens Clinic Hospital, Welch, West Virginia. Paper. Pp. 138. Superior Office Supply, Inc., Department S-60, Box 591, Welch, West Virginia, 1960.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Deauville Hotel, Miami Beach, Fla., Sept. 26–29, 1961.

American Radium Society
Secretary, Dr. Charles G. Stetson, 350 Engle Street, Englewood, N. J. Annual meeting: Broadmoor Hotel, Colorado Springs, Colo., May 10–14, 1961.

Radiological Society of North America
Secretary, Maurice Doyle Frazer, 1037 Stuart Bldg., Lincoln, Neb.
Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual Meeting: Palmer House, Chicago, Ill., Nov. 26–Dec. 1, 1961.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: Roosevelt Hotel, New York, N. Y. Feb. 7–10, 1962.

Section on Radiology, American Medical Association
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: New York City, June 26–30, 1961.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building. Rochester, Minn. The Spring 1961 examination will be held at the Denver Hilton Hotel, Denver, Colorado, June 19–22, inclusive; the deadline for filing applications was January 1, 1961. There will be no Special Examination in Nuclear Medicine. The Fall 1961 examination will be held at the Shoreham Hotel, Washington, D. C., December 4–7, inclusive; the deadline for filing applications is July 1, 1961. A Special Examination in Nuclear Medicine will be offered if there are sufficient applications.

American Association of Physicists in Medicine
Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

Tenth International Congress of Radiology
Secretary-General, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meets in Montreal, Aug. 26–Sept. 1, 1962.

Seventh Inter-American Congress of Radiology
Counselor for the United States, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colorado. The meeting will be held in São Paulo, Brazil, September 3–10, 1961.
Secretary-General, Dr. Walter Bomfim-Pontes, Rua Cesario Motta, No. 112, São Paulo.

Alabama Radiological Society
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

American Nuclear Society
Executive-Secretary, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill.

Arizona Radiological Society
Secretary, Dr. Don E. Matthieson, 926 East McDowell Rd., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. J. B. Scruggs, Arkansas Baptist Hospital, Little Rock, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr. Melvin M. Figley, Department of Radiology, University of Washington, Seattle 5, Wash. Annual meeting to be announced.

Atlanta Radiological Society
Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockly Radiological Society
Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St. Philadelphia, Pa.

Brooklyn Radiological Society
Secretary, Dr. Joseph Arcomano, 168 Clinton St., Brooklyn 1, N. Y. Meets first Thursday of each month October through May.

Buffalo Radiological Society
Secretary, Dr. Kenneth H. Seagrave, 537 Delaware Ave., Buffalo 2, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Radiological Society
Secretary, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary, Dr. Robert L. Freidman, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. William F. Hutson, 5145 N. California Ave., Chicago, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary, Dr. Norman E. Berman, 14404 S. Park Blvd., Shaker Hgts. 20, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

Colorado Radiological Society
Secretary, Dr. Bertram L. Pear, 3705 East Colfax Ave., Denver 6, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. James L. Krieger, 85 Jefferson St., Hartford, Conn. Meets first Friday in February and April.

Dallas-Fort Worth Radiological Society
Secretary, Dr. F. J. Bonte, 5201 Harry Hines Blvd., Dallas 35, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit 1, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

East Tennessee Radiological Society
Secretary, Dr. J. Marsh Frere, Jr., 205 Medica Arts Building, Knoxville, Tenn. Meets in January and September.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Eastern Conference of Radiology
Secretary, Arrangements Committee, Dr. Philip Myers, Baltimore City Hospital, Baltimore 24, Md. Annual meeting to be announced.

Eastern Radiological Society
Secretary, Dr. John D. Osmond, Jr., Euclid-Glenville Hospital, Cleveland 19, Ohio. Meets at Mid Pines Club Southern Pines, N. C., April 16–19, 1961.

Florida Radiological Society
Secretary, Dr. Alfred G. Levin, 837 DuPont Bldg., Miami, Fla. Meets twice annually, in the spring with the annual State Society Meeting, and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

Georgia Radiological Society
Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Miami Radiological Society
Secretary, Dr. Donald H. Altman, 2751 Coral Way, Miami, Fla. Meets monthly third Wednesday at 8 P.M. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary, Dr. William E. Powers, St. Louis, Mo.

Houston Radiological Society
Secretary, Dr. John Douglas Reeve, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. Claude W. Barrick, St. Alphonsus Hospital, Boise, Idaho. Meets in the Spring and Fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. David E. Wheeler, 1500 North Ritter, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary, Dr. Lewis G. Allen, 807 Huron Bldg., Kansas City, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. Lawrence A. Davis, 226 East Chestnut St., Louisville, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Walter Stilson, 1720 Brooklyn Ave., Los Angeles, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Albert A. Poulin, Thayer Hospital, Waterville, Maine. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

Memphis Roentgen Society
Secretary, Dr. Hollis H. Halford, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. Joseph F. Wepfer, 5000 W. Chambers St., Milwaukee 10, Wis. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

Mississippi Radiological Society
Secretary, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. J. K. Boughn, 35 11th Ave., Helena, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Alan E. Baum, 100 Nowbridge Rd., Hicksville, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. Ronald E. Waggener, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Nebraska. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through May at The Longwood Towers, Brookline, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly

New York Roentgen Society
Secretary, Dr. Albert A. Dunn, 622 W. 168th St., New York, N. Y. Meets monthly on third Monday, New York Academy of Medicine at 4:30 P.M.

North Carolina Radiological Society
Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. R. F. Raasch, Post Office Box 990, Dickinson, North Dakota. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Lester I. Citrin, St. Mary's Hospital, Troy, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. Paul D. Meyer, 125 S. Grant Ave., Columbus, Ohio. Annual meeting: Deshler-Hilton Hotel, Columbus, Ohio, May 19–21, 1961.

Oklahoma State Radiological Society
Secretary, Dr. E. D Greenberger, Medical Arts Bldg., McAlester, Okla. Meets in January, May and October.

Oregon Radiological Society
Secretary, Dr. George R. Satterwhite, 1123 S.W. Yamhill, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Portland, Oregon, May, 1961.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Frederick R. Gilmore, 234 State St., Harrisburg, Pa. Annual meeting: Bedford Springs Hotel, May 26–27, 1961.

Philadelphia Roentgen Ray Society
Secretary, Dr. Robert B. Funch, Department of Radiology, Germantown Hospital, Philadelphia 44, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Ross H. Smith, St. Margaret Memorial Hospital, Forty-Sixth St., Pittsburgh 1, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Section, Baltimore Medical Society
Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Society of Greater Cincinnati
Secretary, Dr. Donald Janny, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Philip S. Arthur, 274 Young Hotel Bldg., Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Robyn Hardy, 4324 Magnolia St., New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. Austin J. Tidaback, 912 Prospect Ave., Plainfield, N. J. Meets at Atlantic City at time of State Medical Society meeting and in November in Newark, N. J.

Radiological Society of New York State
Secretary-Treasurer, Dr Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary, Dr. Joseph F. Linsman, 436 N. Roxbury Dr., Beverly Hills, Calif.

Redwood Empire Radiological Society
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Robert H. Greenlaw, 260 Crittenden Blvd., Rochester 20, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Denver Hilton Hotel, Denver, Colo., Aug. 10–12, 1961.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
Secretary, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. M. A. Sisson, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bimonthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. William E. Sheely, 1746 K St., N.W., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

Section on Radiology, Southern Medical Association
Secretary. Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. Richard G. Lester, 412 Union St., S.E., Minneapolis 14, Minn. Annual meeting: Deaville Hotel, Miami Beach, Fla., Sept. 25, 1961.

Society of Nuclear Medicine
Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. *Administrator*, Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Penn Sheraton Hotel, Pittsburgh, Pa., June 14–17, 1961.

South Bay Radiological Society
Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala.

Southwestern Radiological Society
Secretary, Dr. Ralph S. Clayton, 1501 Arizona, Bldg. 2-A, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. James J. Range, P.O. Box 324, Johnson City, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Texas. Annual meeting to be announced.

Tri-State Radiological Society
Secretary, Dr. James R. Mathews, 118 S. E. First St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. Powell G. Dillard, Jr., 715 Church Street, Lynchburg, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Joseph T. Houk, 14303 Ambaum Blvd., Seattle 66, Wash. Meets third Monday of each month from September through April at the University of Washington Medical School.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, 112 N. Woods St., Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Richard P. Avondu, Yonkers General Hospital, Park & Ashburton Ave., Yonkers, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Howard G. Bayley, 116 Iroquois Parkway, Beaver Dam, Wis. Annual meeting each spring in various places.

X-Ray Study Club of San Francisco
Secretary, Dr. John H. Heald, 450 Sutter St., San Francisco 8, Calif. Meets monthly, third Thursday at 7:30 P.M., Children's Hospital, September through June.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Julio Toriello, 11 Calle 2-37, zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vega Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15. México 7, D. F.
Secretary-General, Dr. E. Alvarez Hernández. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. César E. Rosa-Perez, Fondo del Segura del Estado, Parada 1, San Juan 8, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin. Quest, Montreal, Que. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

Edmonton and District Radiological Society
Secretary, Dr. S. C. Windle, 105 Northgate Bldg., Edmonton, Alberta. Meets first Tuesday of each month, Oct. to May.

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced.

Section of Radiology of the Royal Society of Medicine ((Confined to Medical Members),
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

Canadian Association of Radiologists
Honorary Secretary, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. Jean-Louis Léger, 1555 Summerhill Ave., Montreal 25, Que. Annual meeting: Marlborough Hotel, Winnipeg, Man., Jan. 22–24, 1962.

Montreal Radiological Study Club
Secretary, Dr. F. McConnell, 1650 Cedar Ave., Montreal, Quebec. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Canada. Meets third Saturday each month.

Toronto Radiological Society
Secretary, Dr. L. R. Harnick, Toronto Western Hospital, 399 Bathurst St., Toronto, Ontario. Meets second Monday of each month September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, D. Camillo Segreto, Avenida Angélica, 1.170, Caixa Postal 5984, São, Paulo, Brazil.

Sociedad Argentina de Radiología, Junta Central Buenos Aires
Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Perú. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.
Secretary-General, Dr. Ch. Proux, 9, rue Daru, Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut. Lagenbeckstr. 1, Mainz, Germany. Annual meeting: April 16–19, 1961, in Hamburg.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnen, Violenweg 14, den Haag Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

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ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

Head

Jeppsson, P. G., and Olin, T. Cerebral angiography in rabbit; an investigation of vascular anatomy and variation in circulatory pattern with conditions of injection. *Lunds Universitets Arsskrift.* N. F., Aug. 24, 1960, *25:6*, 1–55. (From: Department of Neurology, The Roentgen-Diagnostic Department and The Institute of Physiology, University of Lund, Lund, Sweden.)

The authors studied the anatomy of the rabbit's brain by angiography. About 70 rabbits of both sexes and weighing from 2.0 to 2.5 kg. were used. The animals were anesthetized with intravenous urethane, with an initial dose of about 2 gm. per kg. of body weight.

The contrast medium used for carotid angiography was urografin 60 or 76 per cent (Schering). The animals tolerated repeated injections of 2 ml. of the 60 per cent medium while the 76 per cent contrast medium sometimes caused convulsions and respiratory standstill. While hypaque 90 per cent (Winthrop) injected into the common carotid artery in 1 case was followed by convulsions and death, the injection of this contrast medium into the sagittal sinus was not followed by any demonstrable untoward reaction. Thorotrast 25 per cent (Heyden) was found to offer no advantages.

When study of the anatomy of the cerebral arteries alone was desired, barium suspension was injected into the internal carotid artery. This suspension was prepared by dissolving a small amount of gelatin powder in hot water and stirring in collobar (Astra), which is finely granular, or lumibar (Pharmacia), which is more coarsely granular, until a fairly thick suspension was obtained. In the investigation of the venous system, red lead was sometimes used as a contrast medium instead of barium sulfate.

On selective injection of contrast medium into the internal carotid artery, the bifurcation of the common carotid artery was carefully exposed, after which the external branches were occluded with clips or were ligated. In those cases in which the injection pressure was measured, an Elema electromanometer was connected into the circuit by a wide branch of rubber tubing placed as closely as possible to the cannula inserted in the carotid artery. A second electromanometer was connected with the femoral artery by means of a polyethylene tube for measuring the blood pressure.

It was found that the internal carotid artery is the first vessel to spring from the dorsal aspect of the common carotid artery. In one-fourth of the animals, the internal carotid artery and occipital artery originated from a common trunk. An anastomosis of varying width between the internal and external carotid arteries connected the internal ophthalmic artery and the maxillary artery. In rabbits, the circle of Willis is, as a rule, well developed. It differs from the anatomy of human beings in only one respect, *i.e.*, the fusion of the anterior cerebral arteries; in man they are connected by a short transverse trunk.

The blood is drained from the brain mainly by the external jugular system through the temporal emissaries from the transverse sinuses. Most of the remainder is drained by the three vertebral veins and only a minor amount by the internal jugular veins and the paravertebral veins.

On selective injection of contrast medium into the internal carotid artery, a complete cerebral arteriogram will be obtained at an injection rate of about 0.1 ml./sec. Investigations demonstrated that the number of arteries visualized increased with the rate of injection, and, when the rate was high, the contrast medium passed over into the internal carotid artery on the other side, into the vertebral arteries and into the maxillary artery on the injected side. The rate of injection and the injection pressure are intimately correlated. Other conditions being equal, a fall of the blood pressure results in the filling of a larger number of cerebral vascular regions.—*J. N. Ané, M.D.*

Currarino, Guido, and Silverman, Frederic N. Orbital hypotelorism, arhinencephaly, and trigonocephaly. *Radiology*, Feb., 1960, *74*, 206–217. (Address: G. Currarino, Elland and Bethesda Avenues, Cincinnati 29, Ohio.)

The relationships between orbital hypotelorism, arhinencephaly, and trigonocephaly are discussed and 2 cases illustrating these three malformations are reported. No normal standards could be found for the interorbital distance in infancy and childhood. The authors therefore proceeded to determine the normal range of this cranial dimension by a study of posteroanterior roentgen projections of the skull in 250 children.

Orbital hypotelorism indicates an abnormal narrowing of the interorbital space. It is often more obvious roentgenographically than clinically. The malformation is a frequent finding in arhinencephaly and trigonocephaly. Arhinencephaly is a family of malformations, the most characteristic feature of which is an absence of the olfactory nerves and often, also, of other parts of the rhinencephalon. The cause of the anomaly is an arrest in the embryologic development of the cranio-fronto-nasal process and the anterior part of the forebrain. Trigonocephaly is a congenital cranial malformation in which a small and pointed forehead, together with a tendency toward an increase in the biparietal diameter, gives the head a triangular configuration. There are two types of this malformation: a simple form in which the cranial deformity is not associated with any abnormality of the brain, and a more com-

plex form occurring in arhinencephaly, in which the rhinencephalon and often other parts of the forebrain are defectively developed. A large percentage of patients with trigonocephaly are otherwise normal.

The presence of orbital hypotelorism, as well as trigonocephaly, should always arouse the suspicion of a maldeveloped rhinencephalon and forebrain, particularly in the presence of other external anomalies such as a deformed nose, an undivided nasal cavity, absence of the premaxilla, a median cleft in the upper lip, microphthalmia, and microcephaly.—*Arno W. Sommer, M.D.*

Stovin, James J., Lyon, James A., Jr., and Clemmens, Raymond L. Mandibulofacial dysostosis. *Radiology*, Feb., 1960, *74*, 225–231. (Address: J. J. Stovin, University Hospital, University of Maryland, Baltimore 1, Md.)

Mandibulofacial dysostosis is a syndrome of congenital anomalies involving the mandible, maxillae and ears which has been recognized in increasing numbers during the past two decades. A total of 59 cases has been reported in the English and European literature with only 3 appearing in the radiologic literature. The authors add 4 cases to this total, reporting studies of 2 brothers and 2 sisters of different families with the syndrome.

The congenital defects associated with the syndrome are multiple. Clinically the most common finding is an obliquely downward slanting of the palpebral fissures, giving an "anti-mongoloid" appearance to the eyes. Frequently there is a notching of the lower lids (coloboma) at the junction of the middle and outer thirds. A constant finding is that of hypoplasia of the facial bones. The malar bones are hypoplastic or entirely absent. The zygomatic arches are incomplete, and the infraorbital ridges are defective and depressed. Microtia and defects of the auricles, stenosis or absence of the external auditory canals, middle ear abnormalities, inner ear defects, and deafness are all present in many cases. A receding hypoplastic mandible with a more obtuse angle than usual, resulting in malocclusion and associated dental problems, is quite common.

Roentgenograms, or reports of roentgenograms, are available for only 24 of the cases which have been reported. The chief roentgen finding is the absence of the zygomatic arches. The maxillae are hypoplastic and the antra small. The mastoid portions of the temporal bones are also underdeveloped, the tips being absent and pneumatization lacking. Inner ear abnormalities are also present. The mandible is small and the angle more obtuse than normal.

The etiology of this condition is not known. One theory is that there is an embryologic basis resulting in retardation of, or interference with, the differentiation of the mesoderm at the 50 mm. stage of development. Another quite different theory places the cause on a vascular basis, with absence of the stapedial artery. The hereditary component of this syndrome is stressed by some authors. Of the 63 cases studied for this report, in 27 there were definite or suggestive findings in relatives along both ancestral and collateral lines. It is thought that the syndrome appears to follow an irregular form of dominant transmission.

The authors feel that with a careful roentgenologic examination and analysis the radiologist can be of great help to the otologist in planning surgery of the middle and inner ear in the many cases of middle ear deafness seen in this syndrome.—*Donald N. Dysart, M.D.*

Feist, John H., and Gibbons, T. G. Osteochondromatosis of the temporomandibular joint. *Radiology*, Feb., 1960, *74*, 291–294. (Address: J. H. Feist, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.)

The authors report a single case of osteochondromatosis of the temporomandibular joint. They consider this to be the first to be reported.

The characteristic roentgenologic findings were a calcified body in the joint space and a second semicircular body in the space between the coronoid and the condylar processes of the right mandible. Scattered intervening calcifications were present. The left temporomandibular joint appeared normal. Upon surgical exploration a freely moveable, loose body was removed from the joint space. Histologic examination showed this to be osteocartilaginous in nature. The postoperative roentgenogram and laminagram demonstrated the previously noted semicircular body between the condylar and coronoid processes. Another smaller densely sclerotic body which was interposed between the condyloid fossa and the condylar process was observed and was thought to represent a recurrence of the previously excised lesion, or a third body not observed preoperatively, or a remnant of the base of the resected lesion. The absence of any evidence of body or cortical deformity in the vicinity of the osteocartilaginous bodies indicates that they represent osteochondromatosis rather than multiple osteochondromata. The larger body between the coronoid process and the condylar process, which was not seen at the time of surgery, probably arose from the internal synovial membrane of the synovial sac. The sac was either stretched or perforated by this body because it lay hidden behind the zygoma.

The roentgen diagnosis of temporomandibular joint lesions is difficult because of the various overlapping osseous shadows. Laminagraphic examination is valuable when conventional roentgenography fails to demonstrate a lesion.—*W. M. McBride, M.D.*

Neck and Chest

Agati, G., and Adaglio, L. Sopra alcuni casi di laringocele sintomatico (considerazioni clinico-radiologiche.) (Some cases of sympto-

matic laryngocele [clinico-radiologic considerations].) *Ann. radiol. diag.*, 1960, *32*, 464–489. (From: Istituto di Radiologia dell 'Università, Torino, Italy.)

Symptomatic laryngocele is the result of abnormal dilatation of the appendage of the ventricle of Morgagni. This entity was first reported by Larrey in 1829. The authors describe the roentgen findings in these cases of herniation of the larynx.

The herniation, which retains its communication with the larynx, is filled with air. This condition must be differentiated from a laryngeal cyst, which is an abnormal developmental anomaly. Predisposing factors are industrial or professional occupations involving such activities as glass blowing, wind instrument playing, singing, etc.; also, inflammatory or neoplastic processes in this area may permit formation of a ball valve mechanism.

Internal laryngoceles are dilatations of the appendage but they are enclosed by the laryngeal cartilage and the hyothyroid and cricothyroid membranes. The external laryngocele has passed through these tissue barriers and extends into the soft tissues of the neck. The mixed type has features of both. Laryngoceles may involve any surface of the ventricle and may be either unilateral or bilateral.

The highest incidence is found in the adult males who are subjected to endolaryngeal hypertension. Symptoms vary and include: dysphonia, dyspnea, dysphagia (especially with liquids) and reflex cough. The external type also exhibits a soft tissue mass in the neck which is soft and reducible and which is reproducible by increasing intralaryngeal pressure.

Laryngoscopic examination will reveal the laryngocele and its point of origin as well as inflammatory changes of the mucous membrane.

Roentgen examination requires only routine anteroposterior and lateral roentgenograms of the neck with laminagrams in the anteroposterior view. The lateral view is used to detect the internal laryngocele; anteroposterior projections and laminagrams will demonstrate the external or mixed type.

Five cases with illustrative roentgenograms are included in this article. Three of these cases were associated with malignant tumors of the larynx, 1 with tuberculous granulation and 1 with chronic hypertrophic granulation tissue, which was nonspecific.

Roentgenographic studies of the larynx have been more or less neglected in the past and perhaps more attention should be given to this structure.—*Peter E. Russo, M.D.*

Kaye, J., and Thomas, R. G. The problem of abnormal radiological lung patterns. *Med. Proc.*, July, 1960, *6*, 323–332. (From: Department of Radiology, Johannesburg Hospital and Pulmonary Unit of the Department of Medicine, Witwatersrand University, Johannesburg, South Africa.)

A detailed investigation of varying roentgenographic lung patterns was made and correlated with clinical, histologic and historic facts in each case. The following classification is given:

I. Alterations of the normal lung pattern
   a. Increased prominence
   b. Decreased prominence
II. Adventitious pulmonary patterns
   a. Circular shadows
      1. Granular or punctate (ground glass)
      2. Miliary (2 to 4 mm. in diameter)
      3. Nodular
   b. Linear shadows and patterns
      1. Hairlines (Kerley "B" lines)
      2. Crayon lines (bronchiectasis)
      3. Poorly defined lines
   c. Combinations of linear and circular shadows

Roentgen studies included both posteroanterior and lateral projections in deep inspiration and at the end of forced expiration. Laminagrams were used to differentiate the hyperinflation of asthma from organic vascular bed obliteration in emphysema. Axial transverse laminagrams were made to judge lung volume in patients with marked kyphoscoliosis.

However, the authors agreed that roentgen patterns overlap, and the anticipated conclusion was reached that, in the vast majority of cases, it has been their experience that it is impossible to give a definite diagnosis on the roentgen features of altered lung pattern alone. Pulmonary function tests, clinical and laboratory investigations, and historical survey are necessary adjuncts in arriving at a correct diagnosis in pulmonary disease.—*Arch H. Hall M.D.*

Garland, L. H. (San Francisco, California.) A three-step method for diagnosis of solitary pulmonary nodules. *Canad. M. A. J.*, Nov., 1960, *83*, 1079–1082.

The author describes a three step method for the preoperative or nonsurgical diagnosis of solitary pulmonary nodules by which it has been possible to differentiate benign from malignant lesions in almost 90 per cent of 115 cases. A "solitary pulmonary nodule chart" has been prepared by the author and is reproduced in the original article.

While solitary pulmonary nodules may represent many diseases and anomalies, the essential differential diagnosis is concerned with whether the nodule in question is benign or malignant. In the author's series of 2,000 cases, 44 per cent were granulomas; 24 per cent were benign lesions; 26 per cent were primary malignant lesions; and 6 per cent were metastatic malignant lesions.

The "First Step" consists of a complete roentgen survey including stereoscopic roentgenograms of average and heavy densities (as indicated) in routine and special positions, laminagraphy and fluoroscopy. Fluoroscopy permits study of variation in size and affords an opportunity for the radiologist to see and

speak with the patient. Heavy density roentgenograms and laminagrams aid in detecting calcium and cavitation.

The majority of the primary malignant tumors have indefinite, irregular or fuzzy borders. The majority of the benign tumors have relatively sharp borders. A primary bronchial carcinoma may have a sharp border if the lesion is smaller than 1 cm. in diameter.

Small linear densities connecting the nodular opacity and the pleura or the hilus are more common in inflammatory than neoplastic disease. Satellite nodular lesions may be present with both primary carcinomas or granulomas.

Marginal calcification may occur in benign as well as malignant lesions. Centrally located calcification is of much greater diagnostic value and is usually seen in benign tumors only. Primary carcinoma may arise behind a calcific residue of previous infection.

Cavitation associated with a thick or irregular wall is suggestive of neoplasm. A change in the size or shape of the cavitation is not specific for either benignancy or malignancy. The absence of change over a long period of time is suggestive of benignancy. Increase in size over a short period suggests malignancy. In 80 per cent of cases of bronchial cancer, the lesions were not visualized on roentgenograms made one year before their diagnosis.

The "Second Step" includes four clinical considerations: age, sex, presence or absence of thoracic symptoms, and history of recent thoracic tap or surgery. The frequency of bronchial cancer increases after the age of forty-five. It is about five times greater in males than in females. Absence of symptoms favors the possibility of neoplasm. Recent surgery or needling may result in small intrapulmonary hematomas resembling solitary nodules. Lipid pneumonia may be present as a solitary nodule.

The "Third Step" consists of the evaluation of laboratory data. Laboratory examinations such as skin tests and sputum studies are of value in persons under forty years of age. Skin or complement-fixation tests for tuberculosis, coccidioidomycosis and histoplasmosis and sputum tests for tubercle bacilli and tumor cells are suggested. Sputum or bronchial wash cytologic study is rarely positive, except in very large neoplastic nodules.—*J. N. Ané, M.D.*

Ten Eyck, Edward A. Subpleural lipoma. *Radiology*, Feb., 1960, *74*, 295–297. (Address: 525 E. 68th St., New York 21, N. Y.)

Lipomas are rare in the thoracic cavity and are usually related to the mediastinum. Even rarer is the occurrence of subpleural or parietal fatty tumors unconnected with the mediastinum, but the author reports 3 seen in the past five years.

Most intrathoracic lipomas are asymptomatic densities discovered on routine chest examination. They consist of fat lobules of the same composition as ordinary fat and usually are demarcated by a thin fibrous capsule. On chest roentgenograms they appear as areas of increased density in contrast to the aerated lung, but in denser tissue such as muscle they appear as areas of lesser density. Laminagrams were not helpful in the diagnosis in the author's 3 cases, but he suggests that a diagnostic pneumothorax will differentiate as to whether a tumor is in the pleura or in the lung. The preoperative diagnosis is unlikely unless there is an extrathoracic component; differential possibilities include pleural metastases, pleural fluid loculations, and primary pleural tumors.—*James C. Moore, M.D.*

Litwer, Herman. Myelolipoma of the mediastinum. *Radiology*, Mar., 1960, *74*, 471–473. (Address: Veterans Administration Center, Martinsburg, W. Va.)

Myelolipomas are uncommon tumor-like masses composed of heterotopic bone marrow and adipose tissue. They usually occur in the adrenal gland, but have been reported to have occurred in the retroperitoneal area, and also in the chest. Although they may be present without any evidence of other disease, they are sometimes found in association with severe anemias. This was particularly noted in the 2 cases reported by the author, both of which had congenital hemolytic jaundice. The mediastinal mass observed on roentgenographic examination in both cases appeared homogeneous, sharply defined, and somewhat lobulated. Calcification was not observed. In 1 case the mass extended from the right posterior mediastinum into the right middle and lower lung fields, measuring 13 cm. in its greatest diameter, with a smaller mass in the left lower mediastinum. In the other case reported, the mass was located in the lower posterior mediastinum extending on both sides of the midline. These tumor masses evidently were not producing any deleterious effects.—*W. M. McBride, M.D.*

Sheehan, R., Lessmann, F., Marchetta, F., and Lin, R. K. Roentgenographic and clinical study of larynx and pharynx. *Surg., Gynec. & Obst.*, Dec., 1960, *111*, 753–758. (From: Departments of Diagnostic Radiology and Head and Neck Surgery, Roswell Park Memorial Institute, Buffalo, New York.)

The larynx, with its hollow cavity, has three-dimensional planes. Clinical examination by direct vision allows only one of these planes to be observed adequately. The other two can be studied by lateral roentgenograms and anteroposterior laminagrams.

The first laminagraphic study of the larynx made with reference to carcinoma was reported in 1937 by Gunsett. Since then many fundamental investigations on the physiology, topography, and pathol-

ogy of the larynx have been made. The roentgen anatomy and laminagraphic appearance of the larynx are well understood now, but there are still limitations of this procedure and difficulties in interpretation.

The material of the authors consisted of 60 patients and analysis of films was made by two radiologists who had no clinical information. It was found that clinical examination and roentgenologic studies supplement each other and are indispensable in correct diagnosis of lesions of the pharynx and larynx. Laminagrams were found to yield additional information in large tumors of the pharynx which extended into the endolarynx and obscured direct vision of the cords. In cases in which the lesion was confined mainly to the cords, subglottic extension was demonstrated on the laminagrams.

This survey revealed a close correlation between roentgenologic and clinical findings.—*Richard E. Kinzer, M.D.*

Morris, Roy. (Johannesburg, South Africa.) Dysphagia lusoria presenting as superior mediastinal syndrome. *Brit. M. J.*, Nov. 26, 1960, *2*, 1558–1561.

In 1787 Dr. David Bayford carried out a necropsy on a woman who died of starvation, after having suffered from dysphagia from the age of 13 to 60. He found an aberrant subclavian artery, which arose from the left side of the aortic arch and coursed between the esophagus and the trachea to supply the right arm. He concluded that the anomalous vessel had pressed upon the esophagus, causing dysphagia. He applied to this disorder the name of dysphagia lusoria, lusus naturae, meaning a freak of nature.

Dysphagia lusoria in infancy signifies esophageal compression by any congenital arterial abnormality, while in an adult it usually denotes esophageal compression due to an aberrant right subclavian artery.

In the adult type the right subclavian artery arises from the left side of the aortic arch beyond the origin of the left subclavian artery and courses to the right in one of three ways. It may run behind the esophagus (80 per cent), between the esophagus and trachea (15 per cent), or in front of the trachea and esophagus (5 per cent).

Embryologically, an arteria lusoria represents the persisting distal descending portion of the fourth right aortic arch, there having been obliteration of the proximal arch in reverse of the normal situation. Normally, the fourth right aortic arch forms the right aortic arch, which disappears. Its persistence leads to the formation of an aberrant subclavian artery.

The commonest and mildest symptom is a feeling of food sticking under the manubrium sterni. Dysphagia may be mild and chronic or mild and recurrent. It may become progressively worse.

The diagnosis is usually made with a barium swallow. In the posteroanterior projection with a small amount of barium in the esophagus an oblique defect about 0.5 cm. wide, passing upwards from the left to the right on the posterior aspect of the esophagus just above the aortic arch, is seen. On the posterolateral aspect of the esophagus the abnormal vessel produces a typical notch. If the vessel runs in front of the esophagus a similar posteroanterior appearance is noted but in this case the notching will be anterior. Should the vessel course in front of the trachea, no esophageal defect will be encountered. There may, however, be a prominence of the left mediastinal shadow of the pulsatile nature.

Other methods of examination used are angiography and esophagoscopy.

The author concludes that adult dysphagia lusoria is due to an aberrant right subclavian artery compressing the esophagus. This disorder is probably not as rare as the paucity of case reports would suggest. He describes a case in which complete disappearance of the symptoms and signs occurred after surgical resection. He also states that this is the first known adult patient to be operated upon for this condition. —*C. Peter Truog, M.D.*

Steiner, R. E., Laws, J. W., Gilbert, J., and McDonnell, M. J. Radiological lung-function studies. *Lancet*, Nov. 12, 1960, *2*, 1051–1055. (From: Hammersmith Hospital and Postgraduate Medical School of London, London W.12, England.)

Believing that the function of a localized area of the lung may be studied by correlating density variations with simultaneous spirometric recordings, the authors present a method of measuring and recording the changes in roentgenographic lung density during respiration.

Using a Philips image-intensifier, the patient is fluoroscoped and the sites for examination selected. These are usually bilaterally symmetric circles, 5 cm. in diameter, located immediately below the clavicles and just above the diaphragmatic domes. A two-channel linear recorder is used, with one pen connected to the logarithmic amplifier of the photomultiplier which records the roentgenographic density, while the second pen records the position of the spirometer bell through a variable linear resistor. Recordings are made of breathing at an ordinary rate and amplitude, on deep respiration, and on forced expiration after full inspiration.

The alterations in lung density during respiration are a function of the degree of expansion of the part of lung under observation, and hence the amount of air exchanged. The results so far indicate that the density curves are usually symmetric in comparable areas of each lung and there is good correlation, both in timing and amplitude, between the spirometric and density curves. If there is unilateral lung disease, reference to the normal side simplifies the analysis

of the curves. When the disease is bilateral, comparison has to be made with normal controls.

As the two curves are normally synchronous, any deviation implies localized air-flow obstruction, or even reversal. When alterations in lung density occur without spirometer movement, intrapulmonary air flow must be taking place. When there is localized air trapping, the densitometric tracing may show a slow rate of loss of density even though the spirometer tracing may be relatively normal.

Further studies are planned to assess this procedure's place among other more conventional lung-function tests.—*Donald M. Monson, M.D.*

McMyn, J. K. Radiological appearances of pulmonary hypertension. *J. Coll. Radiol. Australia*, June, 1960, *4*, 21–28. (From: X-Ray Department, Green Lane Hospital, Auckland, New Zealand.)

The author has attempted to correlate the roentgenologic findings in 56 cases of mitral stenosis and to compare them with the catheterization findings or the pressures found at operation. He concludes that Kerley's B lines, now called septal lines, are a valuable sign of pulmonary venous hypertension. They do not establish its degree except that the pressure tends to be over 20 mm. Hg. When they are present, there is often a raised pulmonary artery pressure. However, there is not a close relationship between septal lines and pulmonary arterial pressures. The absence of septal lines does not exclude pulmonary arterial hypertension in mitral disease. Enlargement of the main pulmonary artery indicates pulmonary arteriolar hypertension and gross enlargement suggests high pulmonary artery systolic pressure. There is no correlation between the size of the pulmonary artery and the pulmonary venous hypertension.—*A. E. Childe, M.D.*

Holzel, A., and Fawcitt, J. Pulmonary changes in acute glomerulonephritis in childhood. *J. Pediat.*, Nov., 1960, *57*, 695–703. (Address: Department of Child Health, St. Mary's Hospital, Whitworth Park, Manchester 13, England.)

The authors discuss the pulmonary roentgen findings in 76 patients with acute nephritis. Thirty-seven demonstrated roentgenologically detectable lung lesions. There were two broad categories of findings: the first demonstrated the already well known roentgenologic pattern of pulmonary edema, described in the adult as being associated with uremia or with azotemic edema; the second demonstrated partial collapse, consolidation, interlobar and pleural effusions. The interlobar as well as the pleural accumulations of fluid were relatively small and they could only be demonstrated in patients examined during the first week of the illness.

The authors gained the impression that the lung changes appeared in the first week after the onset of symptoms and underwent spontaneous resolution within three to fourteen days after detection. The presence of the lung lesions in the first week of the illness coincides with the development of hydremia and hypertension. The spontaneous and rapid resolution following the onset of diuresis and the free mobility of the pleural fluid suggest that they result from the accumulation of edema. It is feasible to assume that, during the coincident phase of hydremia, edema develops in lung structures supplied by these vessels. This would explain the accumulation of fluid in the pleural cavities and in the interlobar space. The occurrence of lobular or even lobar collapse could be explained as a result of edema of the bronchial mucosa leading to occlusion of the finer ramifications of the bronchioles. The appearance of sharply localized areas of consolidation might well be accounted for by the development of edema in a limited part of the interstitial tissue with an associated effusion into the alveoli.

The hypothesis presented here, that the pulmonary changes are related to alterations in the extracellular fluid volume, is a possibility. An explanation based on inflammatory changes cannot be eliminated.

The study of 65 children with acute nephritis revealed 38 with detectable pulmonary changes on the roentgenograms. There is no correlation with the age of the patients or the degree of azotemia present.—*James F. Martin, M.D.*

Deaton, W. Ralph, Jr., and Doyle, Owen W. Pneumothorax in infants and children. *South. M. J.*, Dec., 1960, *53*, 1487–1494. (From: Surgical and Radiological Services of Moses H. Cone Memorial Hospital, Greensboro, N. C.)

Pneumothorax in infants or children is a rare entity that usually responds readily to treatment. The etiologic agent may be any of those that can produce a pneumothorax in adults. Predisposing factors are thought to be prematurity, difficult delivery, cesarean section and vigorous resuscitative efforts.

The clinical diagnosis of pneumothorax in the newborn may be very difficult. The onset of a significant degree of pneumothorax is accompanied by cyanosis, dyspnea and tachycardia. The physical signs may or may not be present. Roentgenographic examination is the only reliable diagnostic method. Other conditions that may cause similar symptoms in the newborn are diaphragmatic hernia and a rapidly expanding lung cyst. These usually are also differentiated by roentgenographic study.

The treatment varies from watchful waiting to aspiration or to inter-rib thoracotomy, or to even open thoracotomy.

Seven cases are presented with their accompany-

ing roentgenograms. The entities associated with the pneumothorax in this series are spontaneous pneumothorax in the newborn, tension pneumothorax associated with staphylococcic pneumonia, operative pneumothorax following tracheostomy, and obstructive emphysema pneumothorax following the inhalation of a poison. Regardless of the etiology, treatment is usually successful if the underlying condition can be controlled.—*John L. Gwinn, M.D.*

Ettman, Irving K. Demonstration and localization of valvular calcification by planigraphy. *South. M. J.*, Dec., 1960, *53*, 1529–1533. (From: Department of Radiology, Veterans Administration Teaching Group Hospital, Memphis, Tenn.)

Since the advent of cardiac surgery many patients are now referred for roentgenologic demonstration of calcification of cardiac valves. Calcifications of aortic valves may confirm the diagnosis of aortic stenosis even when there is an associated mitral stenosis which dominates the picture

While fluoroscopy has been long recognized as a means of demonstrating valvular and other intracardiac calcifications, this is not a useful method of recording the findings. Twenty-five cases were selected and studied in an effort to determine the roentgenologic method best suited to demonstrate and localize valvular calcification.

The conventional chest roentgenogram and even the "over-penetrated" film of the chest were discarded in favor of laminagraphy as an accurate means of visualizing and identifying calcification in the aortic and mitral valves. The left anterior oblique view separates the valves so that the aortic valve is in the middle third of the heart shadow and the mitral valve in the posterior third and at a lower level. Layers are cut at 1 cm. intervals from the 6 to 12 cm. level.

The findings in representative cases are presented in 6 figures, but unfortunately the reproductions are not good enough to actually show the calcifications. —*Richard E. Kinzer, M.D.*

Wullstein, H. L. Combined fluoroscopy and endoscopy of lower respiratory passages and oesophagus. *German Med. Monthly*, Oct., 1960, *5*, 338–339. (Address: Universitäts-Hals-Nasen-Ohrenklinik, Luitpoldkrankenhaus, Würzburg, Germany.)

The author describes a special table with a fluoroscopic image amplifier and a television screen for assisting the endoscopist in the accurate visualization of the lower respiratory passages and esophagus during the removal of foreign bodies.

This procedure certainly is much easier than the old method of trying to direct the endoscopist with just a few glances through the old biplane fluoroscope. The patient, however, is anesthetized and respiration is assisted by cuirass ventilator which is used instead of an iron lung.

The amount of radiation to the patient is also much less due to the image amplifier and, of course, the entire procedure is carried out in a lighted room. —*E. S. Carey, M.D.*

Abdomen

Cox, H. T., and Allan, W. R. The dumping syndrome: clinical and radiological aspects. *Lancet*, Dec. 10, 1960, *2*, 1261–1263. (From: Withington and Wythenshawe Hospitals, Manchester, England.)

This paper is based on an experience with 500 cases who had had an elective gastric operation in the past six years. It deals with the clinical aspects of the dumping attacks which may follow the ingestion of certain normal foods, and with the roentgenologic appearances during them. The authors have not used hypertonic glucose to produce the symptoms.

The patients were classified in two main groups: in one, the attack is brought on by a large meal; in the other by particular foods. The authors are concerned in this investigation with the patients whose dumping attacks are brought on by particular foods.

Clinical Features. The patients who gave a clear history of dumping attacks brought on by particular foods were invited to attend as outpatients, and were given these foods. Two points were considered to be important: first, the attempt to produce the attack should be carried out in a room at or above average ward-temperature; secondly, the patient must not lie down after eating but should walk slowly up and down.

The authors reproduced fifteen attacks of dumping in the past six years, and these notes are based on their observations. They found that the outstanding symptom of the dumping attack is profound weakness usually associated with light-headedness. All other symptoms are relatively minor. The symptom is described by the patient as "feeling awful," "as if all the use had drained out of me," and, "as if I were going to die." During a severe attack of dumping, the patient is totally incapacitated. If he continues to walk during the attack, he staggers and falls to the ground. He usually lies down, not to relieve the attack, but simply because he cannot stand up. The vertigo of which he is said to complain is not a true vertigo, but a sensation of being light-headed. The most severe attacks include ocular symptoms. These have been described by the patient as an inability to focus, a blurring of vision, the presence of dark shadow in front of the object looked at or a sensation of seeing things as if far away. A patient was given a newspaper to read. She was quite unable to read the small print, but could read the headlines.

Recumbency delays or prevents the onset of the

dumping attack, a vertical position does the opposite. The interval between taking particular foods and the onset of the dumping attack varies from two minutes to twenty minutes.

Most patients become drowsy and irritable when the attack is passing off. Vomiting was noted only once, a small amount of bile being returned. No diarrhea has occurred in relation to the dumping attack.

Roentgenologic Examination. Six patients were studied during natural dumping attacks. A preliminary examination after barium swallow outlined the gastric stump, stoma, duodenum or jejunum (according to the type of gastric operation). The patient was given the food responsible for the dumping and he was made to walk slowly up and down. He was rescreened at intervals and on the first symptoms of the attack a complete roentgenologic examination was done. If necessary, he was given a further swallow of barium. Immediately after the attack had passed off, more roentgenograms were taken following further barium swallows (if necessary). Two sets of controls were used.

The preliminary examination in all 6 patients showed a normal outline of the gastric stump, stoma, and upper jejunum and the duodenum, with the usual rapid emptying and hyperperistalsis.

The screening in the 4 patients with severe attacks of dumping showed complete stasis and dilatation, affecting the gastric remnant, duodenum and jejunum. All forward movement ceased. The appearance and disappearance of these changes coincided with the start and finish of the dumping attack. The 2 patients with less severe attacks showed similar changes but to a lesser degree. All roentgenograms taken immediately after the attack revealed complete return to the normal emptying and normal hyperperistalsis as demonstrated in the preliminary examination.

The authors conclude that dumping attacks after subtotal gastrectomy may be brought on by eating specific foods—milk, milk puddings, eggs, fatty foods, chocolates, and pastries. A severe attack may incapacitate the patient. Walking, especially in a warm atmosphere, and taking foods that are hot increase the severity of the attack.

Roentgenologic examination during attacks shows stasis, dilatation and no peristalsis in the gastric remnant, duodenum, and jejunum. The appearance and disappearance of these changes coincide with the start and finish of the attack. The worse the attack, the more striking are these changes.—*C. Peter Truog, M.D.*

Stuart, Charles. Perforated peptic ulcer; radiological review of 50 consecutive cases. *J. Coll. Radiol. Australia*, June, 1960, *4*, 32–38. (From: The Fremantle Hospital, Western Australia.)

The author has reviewed the roentgenographic findings in 50 consecutive cases of this condition. He routinely takes four roentgenograms: chest posteroanterior erect, abdomen posteroanterior or anteroposterior supine and erect and abdomen in lateral decubitus position. In his experience fewer than 5 per cent of the cases are unable to stand for the erect roentgenographic study. The whole examination takes less than fifteen minutes to perform.

In this series there was an 88 per cent accuracy in the demonstration of free gas within the abdominal cavity. However, some leaks were small and difficult to detect. The amount of gas varied considerably and bore no direct relationship to the time interval between perforation and the time of roentgen study, or to the size of the perforation. The second important point in perforations is the presence of free fluid in the peritoneal cavity and evidence of this was seen in most of the author's cases.

The conclusion is reached that this type of examination is of great value in the early diagnosis of perforated peptic ulcer.—*A. E. Childe, M.D.*

Strandjord, N. M., Moseley, R. D., Jr., and Schweinefus, R. L. Gastric carcinoma: accuracy of radiologic diagnosis. *Radiology*, Mar., 1960, *74*, 442–451. (Address: N. M. Strandjord, Department of Radiology, University of Chicago, Chicago 37, Ill.)

The authors have studied 283 cases of gastric cancer to determine the accuracy of the roentgenologic diagnosis. In all cases the roentgenograms, cytologic, gastroscopic, and operative reports, surgical pathologic data, and autopsy records were analyzed. The correct diagnosis was made roentgenologically in 219 cases (78 per cent). In 18 (6 per cent) differentiation was not possible. The failure rate was 16 per cent, but in only 14 of the 46 cases interpreted as failures was the roentgenologic interpretation "normal." Thus, the roentgenologic detection of abnormality was 95 per cent. Cytology was performed in 157 of the 283 cases. Twenty-four (15.3 per cent) were incorrectly diagnosed as normal. Cytology appeared to have its highest accuracy in the same group of cases in which roentgen-ray diagnosis was definitive. Gastroscopy, performed in the 64 cases without a positive roentgen diagnosis, led to the positive diagnosis of malignancy in 38 per cent.

By using all diagnostic techniques, a diagnosis can be made preoperatively in 94 per cent. Roentgen diagnosis holds now, and will continue to hold, a preeminent place in the diagnosis of gastric neoplasm. —*Arno W. Sommer, M.D.*

Melamed, Abraham, Haukohl, Robert S., and Callan, Robert E. Pyloric antral mucosal diaphragm with transpyloric mucosal prolapse. *Radiology*, Mar., 1960, *74*, 452–457.

(Address: A. Melamed, 620 N. 19th St., Milwaukee, Wis.)

The authors review the literature of the 5 previously reported cases of pyloric antral mucosal diaphragm and add a sixth case. This rare, apparently congenital, anomaly probably arises during the embryonic stage of development at a time when the esophagus and stomach are solid for a brief period; the membrane develops at a site where secretion vacuoles fail to develop and no lumen is produced. The submucosa then grows in from the sides to form a ring-like diaphragm. The ultimate anomaly, either atresia, stenosis, or diaphragm, depends on the size and position of the developmental failure.

This diaphragm may cause symptoms immediately after birth or during adult life, apparently dependent on the size and location of the diaphragmatic opening. The roentgenographic examination reveals a smooth luminal narrowing with a diaphragm-like filling defect having a central or eccentric opening. The opening in the diaphragm should vary little, if at all, during roentgenography. Peristaltic waves proximal to the diaphragm produce effacement of the gastric rugae; caudad to the diaphragm, there is a tendency toward development of transpyloric mucosal prolapse. Cephalad movement of the distal mucosa during systole—Golden's phenomenon—is prevented by the diaphragm. Should the symptoms warrant, surgery is the only successful form of therapy.—*John S. Alexander, M.D.*

Michener, William M., Kennedy, Roger L. J., and DuShane, James W. Duodenal ulcer in childhood; ninety-two cases with follow-up. *Am. J. Dis. Child.*, Dec., 1960, *100*, 814–817. (From: Mayo Clinic, Rochester, Minnesota.)

This paper gives a follow-up report on 92 of 109 infants and children with duodenal ulcer observed at the Mayo Clinic in a twenty-year period. The ages of the patients at the time of diagnosis ranged from fourteen days to fourteen years.

The clinical features vary with age at the time of onset. In the newborn, duodenal ulcer is suspected because of hematemesis or passage of blood from the bowel or both, or because of signs of intestinal perforation. In many of the patients under ten years of age, no signs or symptoms typical of ulcer were noted. Abdominal pain was the only common finding, and this seldom bore any relationship to meals. In 35 of the 92 children, the pain did awaken them at night.

Of the 92 children diagnosed as having an ulcer, 53 became asymptomatic within four weeks after beginning of treatment and did not have further difficulty. Thirty-nine had recurring symptoms attributed to ulcer. These recurring symptoms presented within five years or less. In approximately 30 per cent of the patients in whom the diagnosis was made at the ages of five to nine years, there were recurring symptoms, but in those between the ages of ten and fourteen years, there was approximately 50 per cent recurrence. Nine of the 39 cases of chronic or recurring symptoms had surgical treatment some time in the course of their illness. At the time of follow-up, 44 of the 92 patients were fifteen years or older.—*John L. Gwinn, M.D.*

Bluth, Irwin. Gastrointestinal carcinoid tumors; roentgen features. *Radiology*, April, 1960, *74*, 573–580. (Address: Beth-El Hospital, Brooklyn 12, N. Y.)

The subject of carcinoid tumors of the gastrointestinal tract is reviewed and 4 cases are reported. The carcinoid tumor was located in the ileum in 2 of the author's cases, in the ascending colon in 1 case and in the sigmoid colon in the fourth case.

The typical carcinoid tumor may appear as a small submucosal nodule. Less often, it is a polypoid or an annular growth. The epithelium over the tumor is usually intact, although occasionally it may be ulcerated. Carcinoid tumors may occur in any portion of the gastrointestinal tract; but the most common site is the distal portion of the ileum. It is carcinoids in this location which most frequently metastasize and eventually lead to the carcinoid syndrome. The malignant carcinoid syndrome consists of chronic diarrhea, flushing and cyanosis, respiratory distress, and right-sided cardiac disease. It has been described only in the presence of metastatic malignant carcinoids with large numbers of functioning cells, usually in the liver.

It is suggested that all gastrointestinal carcinoids, except those of the appendix, be regarded as malignant.—*Arno W. Sommer, M.D.*

Morgan, Leslie A., and Parks, Raymond E. A double-blind study of oral cholecystographic media; orabilex and telepaque. *Radiology*, Mar., 1960, *74*, 436–441. (Address: L. A. Morgan, 7 West Columbia St., Orlando, Fla.)

The authors report the results of a double-blind study of oral cholecystographic media using telepaque (iopanoic acid) and orabilex (bunamiodyl). The primary purpose of this study was to evaluate by a purely objective method (a) the side reactions and adverse effects of the two agents, (b) the degree of opacification of the gallbladder and bile ducts, and (c) the form and amount of residual material within the gastrointestinal tract.

A total of 187 patients had complete roentgenographic examinations, 92 with orabilex and 95 with telepaque. Comparable doses of the two media were given. Neither the patient nor the physician knew which medium had been ingested when the inter-

views regarding reactions were held or when the roentgenograms were being interpreted.

The results showed that there were approximately 50 per cent fewer side reactions for orabilex than there were for telepaque. A total of 63 various complaints were elicited in the 92 orabilex cases as compared with 122 complaints in the 95 telepaque cases. The degree of density was essentially the same in both series with the number of poorly and nonvisualized gallbladders being the same for both contrast agents. Similarly, no marked difference was noted in evaluating the gallbladders of fair and good visualization, although there was a slightly higher incidence of good opacification with orabilex. The degree of bile duct opacification, achieved only after the fat meal, and the number of patients in whom opacification occurred were statistically comparable. Eighty-nine of the patients who received orabilex, or 96 per cent, showed no residual opacities in the bowel, or only a trace or minimal amount, compared to 27 patients, or 28 per cent, who received telepaque and who showed no opaque residue.

It is the opinion of the authors that orabilex represents the most significant refinement in oral cholecystographic media to date.—*Donald N. Dysart, M.D.*

Cimmino, Christian V. Cholesterolosis. *Radiology*, Mar., 1960, *74*, 432–435. (Address: Mary Washington Hospital, Fredericksburg, Va.)

The purpose of this paper is fourfold: to furnish some background material on cholesterolosis for the radiologist; to review briefly the roentgenologic diagnosis of cholesterolosis; to offer evidence that the cholesterol polyp may be a temporary, "pre-stone" state; and to reaffirm the opinion that cholesterolosis, as suggested by the polyp, is an adequate indication for removal of the gallbladder.

There are thought to be two factors in the production of cholesterolosis: (a) inflammation, usually of low intensity; and (b) elevated bile cholesterol. The reason for the deposition of cholesterol ester, either diffusely in the subepithelial tissues or in focal accumulations within a fold, is not known, as, at times, multiple, small, pure cholesterol stones are found in gallbladders removed surgically with no evidence of any inflammation.

These small focal accumulations in a fold quite often form a polypoid or papillomatous structure projecting into the gallbladder lumen. They may be single or multiple, and characteristically are fixed in position. They may not be evident on a subsequent examination due either to involution or to severance of the stalk, in which case they may be passed on through the biliary passages or remain and form a nidus for stone formation. The concentration of the opaque medium in the gallbladder invariably is excellent and a post-fat meal film is almost always necessary for visualization of these small structures. In the series studied by the author the largest of the filling defects was 5 mm. in diameter. They were found in all thirds of the gallbladder but none were in the extreme fundus. At times, a marked indentation or incisura in the contour of the opacified gallbladder was present. The reason for this was not apparent.

The author discusses 1 patient in whom a fixed filling defect in the opacified gallbladder was seen, but six months later this was gone and several small stones were apparent. Examination of the excised gallbladder confirmed the presence of stones and diffuse cholesterolosis but showed no excrescences of any kind.

It is the opinion of the author that, when multiple fixed defects are seen, the diagnosis of cholesterolosis is reasonably certain; however, when a single fixed defect is present, the patient should have surgery as there is always the chance that a premalignant or frankly malignant lesion exists.—*Donald N. Dysart, M.D.*

Kaye, J. Preparation of the colon for radiological investigation; using a new laxative. *Med. Proc.*, Oct., 1959, *5*, 458–463. (From: Radiological Department, Johannesburg General Hospital, Johannesburg, South Africa.)

A new contact laxative has been developed in Europe during the past few years. It is available here under the trade name "dulcolax." It is a pure, crystalline compound, tasteless, odorless, colorless, and insoluble in water and alkalis. It is a methane compound (4,4-diacetoxy-diphenyl-pyridyl-2) which is not absorbed into the blood stream and has no action via the systemic circulation. It is thought to act directly on the colon through a local reflex arc. It has little or no effect on the small bowel.

Among other attributes it has been found not to irritate colon mucosa even after prolonged administration with large doses. Satisfactory evacuations in cases of megacolon have been reported. There are no apparent contraindications to its use other than the acute surgical abdomen.

A series of 150 patients was evaluated after using dulcolax preparation of the bowel. The new laxative was found to be more effective in removal of gas and feces from the colon than the bowel washouts, enemas, and laxatives employed in controls. Patients rarely complained of cramps or excessive bowel action when taking the tablets or suppositories.

The following dosage schedule is recommended: three tablets are taken the evening before the colon examination; a suppository is used one hour before the roentgen study. For patients who are very constipated, an additional two or three tablets may be given two days before the examination. Dosage is

reduced if diarrhea is present. Enemas are eliminated.—*Arch H. Hall, M.D.*

Kissel, P., Collesson, L., Dureux, J.-B., Rauber, G., and Anthoine, D. (Nancy, France.) Le mégadolichocolon saturnin. (Saturnine megadolichocolon.) *Presse méd.*, Oct., 1960, *68*, 1739–1742.

Lead poisoning can cause megacolon, either segmental or complete, and the distention can persist for months after treatment and the disappearance of symptoms. The authors contribute 2 cases similar to the longer series reported by Levrat and others. This saturnine (lead) megacolon can give the appearance of an idiopathic type; properly, however, it should be classified with the functional megacolons of toxic origin, of which morphinism provides another example.—*Frank A. Riebel, M.D.*

Trenta, A., Coucourde, F., Birarelli, B., and Schifino, A. Considerazioni clinico-radiologiche sulla rigenerazione della colecisti. (Clinical and radiological considerations on regeneration of the gallbladder.) *Ann. radiol. diag.*, 1960, *33*, 233–243. (From: Istituto di Radiologia dell 'Università di Pavia, Pavia, Italy.)

The authors based their studies on 160 patients who had had cholecystectomy. Intravenous injection of an opaque medium was given to visualize the biliary tract and films were exposed at 20, 40, 120 and 180 minute intervals.

From these studies the authors concluded that the remnant of the cystic duct becomes enlarged in any condition which dilates the entire biliary tract, such as in cases of an impacted stone in the common duct or spasm or scar tissue contraction at the sphincter of Oddi. This may also occur when there has been incomplete removal of the neck of the gallbladder.

Reflux of contrast medium into the duodenal cap may be misinterpreted as being within the biliary tract.

The authors feel that the terms "regeneration" and "pseudoregeneration" of the gallbladder should be eliminated, since proof is lacking that these processes occur.—*Peter E. Russo, M.D.*

Gynecology and Obstetrics

Gros, C. M., Weill, F., and Renaud, R. L'exploration radiologique sans préparation du placenta praevia. (Radiologic examination of placenta previa without preparation.) *J. de radiol., d'électrol. et de méd. nucléaire*, Oct., 1960, *41*, 556–562. (From: Service central de Radiologie, Hôpital civil de Strasbourg, France.)

In the examination of placenta previa, the usual techniques applied to soft tissue studies are not applicable. The considerable thickness of the abdomen in pregnancy would necessitate too long an exposure if, for example the factors used in mammography were utilized. In consequence, a kinetic blur would be inevitable, the roentgen-ray tube would be greatly overloaded, and the patient would receive a dangerous dose.

If more penetrating roentgen rays are used with an appropriate exposure time, the anteroposterior roentgenogram is satisfactory, but the lateral roentgenogram taken with the patient in an erect position is unsatisfactory because the absorption gradient between the soft abdominal parts and the pelvic structures is too great. To obviate this discrepancy, two different exposures may be used but, in obstetric radiology, the number of roentgen studies should be reduced to a minimum.

There are two ways of resolving these problems: the use of a differential filter, or logEtronic reproduction. The authors have combined the two with successful results. They have devised a triangular filter, fitted to the roentgen-ray tube when the lateral roentgenogram is taken; the thickest portion of the filter covers the superficial soft parts of the abdomen, which are very radiolucent, while the thinner portion of the filter faces the prevertebral region, which is of greater density. The posterior lumbopelvic area, which is very opaque, is not covered by the triangular filter.

This filter is placed at the level of the tube-diaphragm, which is 15 cm. from the focus. Film-focus distance is 100 cm. and, at 100 kv., the maximum filtration of the triangular filter is 30 mm. Al. The thickness of the mesial part of the filter is 14 mm. In its thickest part the filter absorbs 93 per cent of the rays, and in its thinnest part, 75 per cent. With 100 kv., an exposure at 175 mas. is usually necessary for the lateral roentgenogram.

The authors first take a roentgenogram with the patient in a standing lateral position, and, if a normally located placenta is seen, the examination is terminated. If not, an anteroposterior roentgenogram is also taken. Sometimes, a study using a localizing cone will complete the examination. The films are then reproduced logEtronically.

Using a high kilovoltage, the dose to the fetus is greatly reduced. The authors' measurements show a skin dose of 2.5 r in the center of the field for the anteroposterior projection and 0.3 r in the lateral projection with the triangular filter interposed.

Normally, the placenta appears on the lateral roentgenogram in the mid-upper pole of the uterus, but rarely posteriorly or anteriorly. The placenta shadow varies in thickness from 2 to 5 cm. according to its position in the upper pole or slightly lateral to it. This shadow is composed of the placenta and of the uterine wall, which is about 1 cm. thick. When

the placenta is laterally inserted, its aspect is similar and is seen only on the anteroposterior roentgenogram.

The diagnosis of placenta previa is based on direct and indirect signs: (1) absence of a normal placenta shadow in both anteroposterior and lateral projections; (2) displacement of the presentation, which on the lateral roentgenogram should not be more than 3 cm. from the pubis and not more than 1.5 cm. from the promontory; on the anteroposterior roentgenogram, the presentation is usually central in location; the signs of displacement of the presentation must be carefully evaluated, especially when the gestation is far from term; and (3) direct visualization of placenta previa, which is greatly enhanced by use of the logEtron. Placenta previa centralis produces a definite displacement on the anteroposterior roentgenogram. If located on the anterior margin, the placenta is easily seen on the lateral roentgenogram extending beyond the pubic bone; if located laterally, placenta previa must be searched for by other means than anteroposterior roentgenograms, on which the pelvic bone makes its presence hard to recognize. The posterior marginal location of the placenta is the most difficult to diagnose and its differentiation from the surrounding structures is greatly improved with the logEtron.

In most cases, the study of direct and indirect signs will lead to a correct diagnosis.—*H. P. Lévesque, M.D.*

Rossi, Plinio, Rizzi, John, and de Santis, Victor. Simultaneous lateral placentography. *Radiology*, Feb., 1960, *74*, 298–299. (Address: P. Rossi, Queens General Hospital, Jamaica 32, N. Y.)

Roentgenographic localization of the placenta in the third trimester is described by the authors. This procedure is accomplished by using a routine 14×17 inch cassette loaded with three unexposed films. The cassette is placed so that a lateral view of the patient includes the entire uterus, sacral promontory, and the symphysis pubis. The tube, at a 40 inch distance, with a 4 mm. Al filter and 0.5 mm. oil, is centered 5 cm. dorsally and caudally from the geometric center of the cassette. The exposure factors are 150 mas. and from 100 to 110 kv. peak. The three exposed films receive standard processing. In developing the middle film, which has been shielded from the full effect of the intensifying screens by the films on either side, it is sufficiently underexposed to demonstrate clearly the anterior uterine wall. The other films are sufficiently exposed to show the spine, the posterior uterine wall, and the pelvic bony structures.

This method was used successfully in 25 cases. In no case where the placenta was in the anterior or posterior wall or upper uterine segment was there failure to localize it correctly.—*W. M. McBride, M.D.*

Genitourinary System

Daeschner, C. W., Singleton, E. B., and Curtis, J. C. Urinary tract calculi and nephrocalcinosis in infants and children. *J. Pediat.*, Nov., 1960, *57*, 721–732. (Address: Department of Pediatrics, University of Texas School of Medicine, Galveston, Texas.)

The authors summarize the roentgenographic and clinical findings in 24 infants and children with calculous deposits in the kidney and urinary tract. The presence of calculus was suspected in 6 patients on the basis of hematuria, pain, fever and generalized abdominal pain. In 9 patients, calculous disease was not clearly indicated by the symptomatology. The presence of calculus formation was established by abdominal roentgenographic examination in all of these 15 patients. It was unilateral in 12 patients and bilateral in 3. Complicating conditions, which were associated with nephrolithiasis, include chronic or recurrent pyelonephritis, stenosis at the ureteropelvic junction with hydronephrosis, stasis from muscular paralysis and immobilization, hyperparathyroidism, and bladder neck obstruction.

Vesical calculi were identified in 7 patients. The stones appeared to be primarily in the lower urinary tract in 6 instances. The calculus was asymptomatic in 4 instances and was identified by a roentgenographic survey of the abdomen. Gross hematuria, marked pain associated with micturition, and acute urinary retention were present in 3 patients.

Diffuse calcification of the renal parenchyma occurred in 3 patients. Renal tubular acidosis, excessive vitamin D intake and idiopathic infantile hypercalcemia were listed as possible etiologic factors.

Chemical analysis of the calculus was made and recorded in 14 of the cases. In all but 1 case, the analysis revealed a mixture of many calcium compounds—usually calcium oxalate, calcium phosphate and calcium carbonate. There were no examples of uric acid stones or urates. The stones in most of the 24 infants and children were associated with the combination of infection and congenital obstruction.—*James F. Martin, M.D.*

Rolleston, G. L. Lower urinary tract disorders in children. *J. Coll. Radiol. Australia*, June, 1960, *4*, 15–20. (From: Department of Radiology, Christchurch Hospital, New Zealand.)

At the outset the author admits there is no one subject in urology which is so poorly understood, and concerning which there is such a variation of opinion, as disorders of the lower urinary tract in children. He feels that they are due to either a functional or to an obstructive abnormality. In order to differentiate between these groups by micturition

cystography, it is necessary to obtain information regarding the capacity and tone of the bladder, the presence or absence of vesico-ureteric reflux, the functional anatomy of the bladder neck and urethra during micturition and the ability of the bladder to empty with and without the stretch reflex.

The technique of micturition cystography is described, stressing the fact that the success depends entirely on the cooperation of the child. Most children over the age of four years will cooperate, but in infancy it is necessary to use general anesthesia and obtain the micturition cystogram by manual expression.

When obstruction is present, residual urine is due to failure of bladder contraction. In functional disorders there is a false residuum due to a ureteral residue. The bladder capacity is often smaller than normal when there is obstruction, although it will show a considerable increase when the bladder musculature dilates. The capacity of the bladder is usually greater than normal in functional disorders. Trabeculation of the bladder is characteristic of obstruction. Ureteral reflux occurs only in the presence of bladder dilatation when obstruction is present; yet, it is frequently observed in functional disease particularly during micturition. Contractions of the ureters tend to be sluggish in obstruction but in functional megaureter they are vigorous and purposeless. In functional disorders the diameter of the bladder neck or urethra is normal; when obstruction exists the diameter is decreased.—*A. E. Childe, M.D.*

Conger, Kyril B., and Toub, Louis. Obstruction of bladder neck in male infant and child; present concepts of diagnostic methods and management, and report of 14 cases. *J. Pediat.*, Dec., 1960, *57*, 855–875. (From: Department of Urology, Temple University School of Medicine and from St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.)

Obstruction of the bladder neck is a common cause of kidney destruction in male infants and children. The disease becomes irreversible unless arrested by relief of the obstruction. Conservative treatment is as harmful as it would be in cases of Wilms' tumor.

Renal secretion begins in the fetal period and obstruction of the bladder neck can produce hydronephrosis incompatible with extrauterine life. There are two extremes: the nonviable newborn infant with completely desroyed kidneys and a young adult with borderline vesical neck contracture and equivocal symptoms. The majority of patients lie between these two extremes, comprising young children with kidney function good enough to sustain life, but obstruction severe enough to cause rapidly progressive renal destruction and failure.

The obstruction can be due to congenital valves of the prostatic urethra, hypertrophy of the verumontanum, contracture of the vesical outlet or hyperplasia of the prostate.

The signs and symptoms vary and may consist only of a slight diminution of the force and size of the stream devoid of proper projectile force, with the infant lying on his back. The severe cases show dribbling, residual urine, a mass in the suprapubic area due to a full bladder, and later fullness in the flank. An infant with a constantly wet diaper or one who gets purple and cries when voiding should be thoroughly investigated.

Relief of obstruction can be obtained by indwelling catheter, suprapubic drainage and later surgery to remove the cause of obstruction. All of these procedures are described in detail.

Cystograms and excretory urograms must be obtained. Demonstration of reflux flow into the ureters on the cystogram indicates obstruction; so does residual urine. The upper urinary tract must also be studied to determine the amount of hydronephrosis.

This article is very enlightening since one tends to forget about vesical neck obstruction in the male infant. Many good roentgenograms are reproduced, and several drawings are included with 14 case reports. Many children with loss of weight, gastrointestinal upsets, acidosis, convulsions or even coma can fit into this group with bladder neck obstruction. To avoid missing the obvious diagnosis, the authors suggest that no male infant be discharged from the nursery until a competent person observes that he voids a good stream and that the mother be instructed to watch for signs of vesical obstruction during his growth period.—*E. S. Carey, M.D.*

Shick, John E., and Shea, James J. Pyeloureteritis cystica; report of a case with spontaneous rupture of the ureter. *Radiology*, Mar., 1960, *74*, 468–470. (Address: J. E. Shick, Henry Ford Hospital, Detroit 2, Mich.)

Pyeloureteritis cystica is the development of multiple, small, submucosal cysts along the upper ureter and pelvis of the kidney. These present roentgenographically as small radiolucent filling defects in this area. The condition is usually associated with a urinary tract infection. As a result of inflammatory changes, there is downward proliferation of the surface epithelium with the formation of epithelial nests beneath the mucous membrane. The central cells of the nests degenerate and small cysts are formed. The diagnosis is usually not difficult and can be made from the intravenous pyelogram but retrograde pyelograms show the cysts to better advantage. Differentiation from nonopaque stones, air bubbles, and blood clots is seldom a problem, while multiple papillomas tend to occur in the lower ureter. However, small pedunculated tumors in the pelvis and tubercu-

lous granulations may be difficult, if not impossible, to distinguish roentgenologically.

The authors report an unusual and interesting case of pyeloureteritis cystica which developed spontaneous rupture of the ureter with extravasation. The patient, a forty-five year old man, was hospitalized with a severe attack of left ureteral colic. A plain roengenogram of the abdomen showed a calculus overlying the left sacroiliac joint and a retrograde pyelogram the following day revealed the calculus unchanged in position. There were typical, beaded radiolucent defects in the upper ureter and pelvis of the kidney. Intravenous pyelography two days later showed the stone 1 cm. lower and, in addition, there was extravasation of the contrast material along the upper ureter due to spontaneous rupture. At ureterolithotomy the retroperitoneal tissue was found to be edematous but no ureteral perforation was found. After removal of the stone the patient made an uneventful recovery.

In the case presented, it is presumed that extravasation was caused by extension of the cysts through the muscular coat and adventitia of the ureter. An intravenous pyelogram two weeks after the above episode showed patency and continuity of the ureter, although there was some irregularity of the upper ureter probably due to residual cysts.—*Edward B. Best, M.D.*

Fister, George M., Nichols, Russell L., Zabriskie, C. V., and Stucki, John F. Dynamic urethrography: cineradiographic method. *J. Urol.*, Dec., 1960, *84*, 733–737. (Address: 704 Eccles Building, Ogden, Utah.)

This is a somewhat different approach to the study of lower urinary tract disease and dynamics than has usually been reported. The authors have studied, by cineroentgenography and spot roentgenograms, the mechanics of voiding and ureteral reflux, and the physiologic anatomy of the bladder base and urethra. They use a combination of opaque contrast medium and carbon dioxide with a simple apparatus which allows them to alternate the media and to inject them under controlled pressure. Contraindications to their procedure consist of urinary tract infection and recent surgical operations on the lower urinary tract.

Premedication in the form of demerol is given shortly before the examination. A 16 to 20F Foley catheter is placed in the anterior urethra and the bag is inflated with 1 or 2 cc. of water. The opaque material and carbon dioxide are connected to a 1 l. aspirator bottle. This bottle is placed at an angle of 26° to the horizontal. The opaque material is allowed to run into the urethra at a pressure of 60 to 100 mm. of mercury, and exposures are made with the cine camera at a rate of 7.5 to 15 frames per second during the injection. Carbon dioxide gas is then allowed to enter the bladder until the patient feels a desire to void. The catheter is removed, the table is put in the erect position, and the act of voiding is studied cineroentgenographically, using 15 to 30 frames per second.

In 2 patients pantopaque marks were placed at the side of each ureteral orifice and at the apex of the trigone. In these 2 patients the act of voiding was recorded with only a small amount of gas in the bladder and with no opaque material used. It was noted that the ureteral orifice moves downward and slightly medially along with the downward movement of the external sphincter during the initial phase of urination. This motion would elongate the intramural portion of the terminal ureter and thus give further mechanical insurance against ureteral reflux.

These studies show that the internal sphincter opens a fraction of an instant before the external sphincter but that the two sphincters act almost in unison at the beginning of voiding. The entire floor of the bladder, the prostatic urethra, and the external sphincter descend approximately 1.5 cm. during the initiation of urination. On voluntary interruption of the urinary stream, the external sphincter closes first. This is followed immediately by contraction of the prostatic portion of the urethra.

Pathologic studies were made on patients with prostatic hyperplasia, urethral strictures, and diverticula. Seven composite illustrations show the equipment and illustrate the various appearances of the lower urinary tract during voiding.—*George W. Chamberlin, M.D.*

Doyle, Owen W. Use of chlor-trimeton to prevent reactions to hypaque in intravenous urography. *J. Urol.*, Dec., 1960, *84*, 776–778. (Address: 1013 Professional Village, Greensboro, N. C.)

The author reports the use of 1 cc. of chlor-trimeton, in addition to the usual dose of 30 cc. of hypaque, for intravenous injection in 600 patients and he compares the reactions to a series of hypaque injections without chlor-trimeton in 200 patients. He found that in the unprotected group 17 per cent had some type of reaction, but in the antihistamine treated patients only 8.3 per cent had an unfavorable reaction. The incidence of typically allergic reactions was reduced 50 per cent by the addition of chlor-trimeton. Vasomotor reactions and pain in the injected arm are nonallergic phenomena and did not differ between the control and experimental groups. Nausea and vomiting were reduced from 50 to 75 per cent and presumably these reactions also occur because of an allergic response.—*George W. Chamberlin, M.D.*

Walsh, Anthony. Hazards of bladder surgery following irradiation. *J. Urol.*, Nov., 1960,

84, 627–629. (Address: 9 Upper Fitzwilliam St., Dublin, Ireland.)

The author reports 1 patient with papillary transitional cell tumors of the bladder. He was treated by transurethral excision and coagulation of multiple bladder areas, following which he was given 4,200 r maximum tumor dose to the bladder. In spite of this therapy, he continued to develop recurrences within the bladder and an attempt was made to do a total cystectomy with an ileal loop transplant connecting the ureters and the prostatic urethra. Subsequently, the patient died and the autopsy findings indicated a definite lack of closure at the sites of anastomosis of the small intestine, of the ureters to the isolated loop, and of the isolated loop to the prostatic urethra.

The author recommends that, when cystectomy has to be performed following radiation therapy, one should abandon any idea of fashioning an artificial bladder attached to the urethra. Furthermore, in such instances, the ureters should be implanted into the isolated loop above the level of the pelvic brim so as to avoid the more heavily irradiated segments of the bowel and urinary tract.—*George W. Chamberlin, M.D.*

Skeletal System

Jeanmart-Michez, Louis. Les localisations osseuses du granulome eosinophile. (Osseous localizations of eosinophilic granuloma.) *J. belge de radiol.*, 1960, *43*, 135–176. (From: Service de Radiodiagnostic de l'Hôpital Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium.)

Four cases of eosinophilic granuloma and 2 cases of Letterer-Siwe disease are presented in detail with good roentgenographic reproductions.

The majority of authors believe that eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease are different stages of the same entity. A recent compilation by Blankoff shows 300 cases of eosinophilic granuloma, 450 cases of Hand-Schüller-Christian disease, 1,150 cases of various kinds of xanthomatosis and about 100 cases of Letterer-Siwe disease.

As to pathogenesis, no definite etiologic factor can be conclusively cited, even though trauma, viral infection, hyperergic allergic reaction, abnormal lipid metabolism, and familial eosinophilic diathesis have all been implicated. Fifty per cent of the cases are noted before the age of twenty.

Osseous lesions are mostly solitary and no particular bone is spared. Loehr in 1947 described phalangeal and metacarpal lesions. Usually, lesions are discovered accidentally, except for temporal or orbital lesions. Transient eosinophilia and, in one-third of the cases, a moderate increase in blood cholesterol can be noted. Histopathologic findings are conclusive as to the diagnosis of eosinophilic granuloma.

The essential roentgen characteristic is total osteolysis of a segment of bone, the lesion being of varying size and shape with clear borders and, subsequently, a peripheral reactive zone of condensation. Lesions in a vertebral body appear at first as osteolytic foci, followed by flattening.

Solitary cysts, all benign and malignant tumors of bones, multiple myeloma, and even inflammatory osteitis, specific or nonspecific, should be ruled out in the differential diagnosis. Cranial lesions and, in particular, metastatic foci present roentgen images very similar to those of eosinophilic granuloma. However, the presence or absence of reactive zones of condensation and the age of the patients help in the differential diagnosis. Differentiation from congenital syphilis is often difficult.—*Jirair N. Sarian, M.D.*

Fisette, J. Lacune corticale fibreuse métaphysaire et fibrome non ossifiant. (Cortical metaphyseal fibrous defect and nonossifying fibroma.) *J. belge de radiol.*, Apr., 1960, *43*, 317–338. (From: Service de Radiodiagnostic, Université de Liège, Belgium.)

The author reports 8 cases of typical nonossifying fibroma of the long bones. He attempts to differentiate two entities, the cortical metaphyseal fibrous defect (Caffey) and the nonossifying fibroma (Jaffé and Lichtenstein), using the size as a differential sign. The former would be small (2 mm. to 5 cm.) and normally would regress, but, if it should get bigger (4 to 7 cm. in its longest diameter), it would be considered a nonossifying fibroma. The same histology is recognized by the author for both lesions. The color varies from brown in early lesions to yellow in older ones and is produced by engorgement with fatty macrophages. He rejects the terms "fibroxanthoma" and "xanthogranuloma" because they lead to confusion.

This distinction between the so-called cortical defect, variously named by Sontag and Pyle (1941), Hatcher (1945), Caffey (1955), and Lefebvre (1956), and the nonosteogenic fibroma of Jaffé and Lichtenstein appears to this reader to be artificial. As a matter of fact, both lesions are the same entity roentgenologically and microscopically. The differentiation offered by the author is redundant and serves no purpose. The term "nonossifying" or "nonosteogenic fibroma" should be retained and its synonym, fibroxanthoma, far from confusing, very aptly labels the lesion as being a tumor composed of fibrous tissue and xanthomatous cells.

The author mentions that in the early phase of the ossifying fibroma, which he calls the cortical metaphyseal fibrous defect, the aspect of the lesion is reminiscent of a periosteal desmoid tumor (Kimmelstiel and Rapp). This is a most important point, which should have been emphasized by the author, because roentgenologically a small fibroxanthoma or nonossifying fibroma may resemble a cortical des-

moid tumor, or conversely. Although they might present a similar aspect on the roentgenogram, clinically the latter usually is painful and most often is located in the distal femoral metaphysis along the linea aspera. Histologically, the periosteal desmoid tumor is composed of a nodule of dense fibrous tissue, arranged in broad whorled fibers, which forms a nidus in the external part of the cortex. Fibroxanthoma is usually not painful and is located within the cortex. Both lesions regress following puberty; but occasionally hyperostosis will develop in a fibroxanthoma.

In the differential diagnosis, the author mentions many entities, such as periosteal desmoid tumor, chronic cortical abcess, eosinophilic granuloma, solitary cyst of bone, mono-osseous fibrous dysplasia, cortical osteoid osteoma, giant cell tumors, periosteal chondroma and, finally, chondromixoid fibroma.

Among the 8 cases which are presented with excellent roentgenographic and microscopic reproductions, 2 cases had been operated on mistakenly, 1 for a painful paresthesia with atrophy of the quadriceps and the other for a tiny effraction at the periphery of a fibroxanthoma considered to be an osteoclastoma.

Although visualization of these lesions is improved by using the tangential projection, all the author's reproductions are in true anteroposterior and lateral views.

This reader considers nonossifying fibroma and so-called cortical defects as different stages of the same process. Usually they regress completely, although sometimes they are followed by osteosclerosis or cortical hyperostosis.—*H. P. Lévesque, M.D.*

Daeschner, C. W., Singleton, E. B., Hill, L. L., and Dodge, W. F. Metaphyseal dysostosis. *J. Pediat.*, Dec., 1960, *57*, 844–854. (From: Department of Pediatrics, University of Texas College of Medicine, Galveston, Texas.)

Abnormalities in conversion of cartilage matrix into bone occur in the primary dysplasia such as chondrodystrophy, or in diseases involving cartilage growth such as hypothyroidism, or in conditions involving deposition of calcium and phosphorus in bone matrix such as rickets or osteomalacia.

In general, certain roentgenographic and clinical features distinguish the chondrodystrophies and certain biochemical as well as roentgenographic changes characterize the osteomalacias.

In this paper 3 cases are presented which roentgenographically exhibited changes in metaphysis without the biochemical changes usually seen, the characteristic alteration being widening of cartilaginous plate with irregularity of metaphysis. The epiphyses were well formed and normal. The provisional zones of calcification were irregular but dense. These changes were more pronounced at the proximal and distal femoral metaphyses but also present in the proximal and distal tibiae, and proximal humeri and distal radii and ulnae. There was some flaring also of the distal ends of the ribs.

Clinically, there was no abnormality other than short bowed legs and increased lumbar lordosis.

Similar cases have been described by Jansen in 1934 and Evans and Caffey in 1958. Fairbanks studying Jansen's case commented that there was no columnar arrangement of the cartilaginous metaphyses as in dyschondroplasia. Evans and Caffey made a similar observation describing their biopsy specimen.

The importance of accurate diagnosis in these cases is stressed since so often they are diagnosed as vitamin D resistant rickets or renal tubular acidosis. If it is realized that "metaphyseal dysostosis" is a new entity, the danger of avoiding the hazards of vitamin D intoxication will be lessened.

In the 3 cases presented the patients had bone lesions suggestive of rickets, without abnormality of the calcium and phosphorus metabolism. This appears to be a form of dyschondroplasia primarily involving metaphyseal bone and producing roentgenographic changes in the metaphysis resembling osteomalacia.

This is a very interesting article in view of the many new changes in epiphyses and metaphyses being described in recent literature. There are photographs of patients plus the pertinent roentgenographic reproductions.—*E. S. Carey, M.D.*

Doyle, James R. Narrowing of intervertebral-disc space in children; presumably infectious lesion of disc. *J. Bone & Joint Surg.*, Oct., 1960, *42A*, 1191–1200. (From: Children's Hospital of East Bay, Oakland, Calif.)

The symptomatology, physical findings, as well as laboratory and roentgenographic findings in 16 children with narrowing of an intervertebral space are presented. A brief review of the literature is also given.

The typical clinical picture in this group is a child between two and four years of age who, for seven or ten days before admission, had symptoms of fever, stiffness of the back, back or hip pain, limp, refusal to sit or stand and night crying. Trauma to the back is frequently noted as is the association of an infection of the respiratory tract or of diarrhea. The child is very irritable and does not like to stand. On examination, severe spasm of the muscles of the lower back is found. A slightly elevated leukocyte count and an increase in the polymorphonuclear cells are present. The sedimentation rate is moderately elevated, but the remaining laboratory findings are usually not informative.

Roentgenograms of the spine at the onset of the symptoms may be negative, but after a period of one or two weeks, the narrowing of the lumbar interver-

tebral space may be observed. As a rule, there is very little involvement of the adjacent vertebral bodies. In very young children, there is gradual widening of the intervertebral space over a period of two to eight months until the involved interspace may be restored virtually to normal. In older children, the intervertebral space does not usually return to its normal height.

This entity is felt to represent an infectious type disorder of the disk. However, in 3 of these patients, either needle aspiration or surgical biopsy was done without any conclusive evidence as to infectious material. With the good blood supply of the intervertebral-disk spaces in children, it does seem reasonable to postulate that trauma to the back in the presence of a transient bacteremia from other causes could localize in the intervertebral disk.

All the patients in this series were treated with bedrest during the acute phase of their illness and the average duration of the bedrest was one month. After the acute symptoms subsided, most of the patients were fitted with some form of back support.However, no striking differences are reported in the results in the patients treated with back supports and those treated without back supports. Antibiotics were given to most patients without any conclusive results.

There are 15 roentgenographic reproductions demonstrating the narrowing of the disk spaces and the improvement with time. There is also one table summarizing the findings in the 16 patients.—*John L. Gwinn, M. D.*

Medlin, Vernon L. Hypertrophic osteoarthropathy in children. *Radiology*, Mar., 1960, *74*, 414–419. (Address: University of Mississippi Medical Center, Jackson, Miss.)

Hypertrophic osteoarthropathy is a disease characterized by clubbing of the digits and ossifying periostitis, primarily of the long tubular bones. It occurs as the sequel of a major visceral disorder, usually intrathoracic in location. It is not infrequently seen in adults, but only 8 cases in children under the age of twelve have been reported to date, and the author adds 2 cases to these.

The roentgenographic findings are primarily limited to the long tubular bones. The distal thirds of the tibia and fibula, and the radius and ulna are usually first involved, with the femur and humerus next in frequency. The metacarpals and metatarsals occasionally are affected. The appearance of the periosteal new bone can vary from a thin line to a marked thickening, and osteoporosis is usually seen when thickening of the new bone is pronounced. The new bone may be 6 to 8 mm. thick and may show layering which possibly represents remissions and exacerbations of the primary condition. The bony changes may disappear with cure of the primary disease.

Differential diagnosis includes specific periostitis as seen with osteomyelitis and avitaminosis, syphilis, and sickle cell disease. Nonspecific periostitis presents the most difficult differential problem, and other aspects of the illness must be considered to make the diagnosis.

The clubbing represents an early stage of the disease and the periosteal changes are an extension of the same process. Pathologic changes consist initially of thickening of the periosteum with infiltration by lymphocytes, plasma cells, and a few polymorphonuclear leukocytes. Then osteoid is laid down, becoming calcified as the inflammatory stage subsides, with the original cortex becoming osteoporotic. All of these changes may be seen in different areas of the same bone at the same time.

Numerous theories of etiology and pathogenesis have been advanced and the disease has been produced experimentally in dogs by anastomosis of the left auricle and pulmonary artery. The most recent theory is that the manifestations of hypertrophic osteoarthropathy are caused by a pulmonary neural reflex mediated by the vagus nerve.— *J. C. Moore, M.D.*

Grand, Milton J. H., Eichenfeld, Stuart, and Jacobson, Harold G. Sacral aplasia (agenesis). *Radiology*, Apr., 1960, *74*, 611–618. (Address: M. J. H. Grand, Montefiore Hospital, New York 67, N. Y.)

Sacral aplasia is of infrequent occurrence and of unknown etiology. The authors present 3 new cases of which 2 were complete and 1 partial. Conceivably, illness, pyrexia, "toxic substances," or heredity may be the causes.

These children have a cone shape to the lower limbs due to neurogenic defects (L-5 to S-5) and atrophic muscles supplied by these nerves. Sensory changes are less common. Orthopedic deformities, usually of the paralytic type, are common. Clubfoot is present in over one-half of the cases, and dislocation of the hips is not uncommon. Clinically, the loss of gluteal masses and gluteal folds is noted; a fat pad is found over the sacral area. Urinary and fecal incontinence is usually present, and in 1 of the reported cases there was a suggestion of a neurogenic colon.—*J. C. Moore, M.D.*

Sgalitzer, M. Zur Röntgendiagnostik der destruktiven Wirbelsyphilis. (The roentgen diagnosis of destructive vertebral syphilis.) *Wien. klin. Wchnschr.*, Oct., 1960, *72*, 714–719. (Address: 1623 Brennen Road, Columbia, S. C.)

In this study, comprising 7 patients, the direct effect of spirochetes on bone is considered rather than the osseous changes which result from tabes and the associated loss of sensation. The roentgenologic

changes occur most frequently in the cervical spine but characteristic signs are also found quite commonly in the lumbar region. The diagnosis of vertebral syphilis can be made with considerable certainty from the following roentgen findings: the anterior portion of one or more vertebral bodies is extensively destroyed and shows a serrated border composed of small osseous prongs directed anteriorly; sclerotic changes are noted in the remaining portion of the vertebral body; hyperostoses and exostoses form bridges between vertebral bodies; spinal ligaments contain a variable amount of calcification; despite the extensive destruction, there is no loss in the height of the involved vertebral bodies. When only a single vertebral body is affected or when the destructive changes are less marked, the diagnosis may have to depend on the presence of typical, luetic involvement of other bones, such as the extremities, or on the dramatic response to antiluetic therapy.

Vertebral syphilis can be differentiated from tuberculous involvement, since the latter condition is characterized by a spotty osteoporosis, collapse of the vertebral body with gibbus formation, involvement of the intervertebral disk, cold abscess, and new bone formation late in the disease. Osteomyelitis causes a marked osteoporosis (sclerosis is a late manifestation), wedge-shaped deformity and abscess formation. Lymphogranuloma also produces changes similar to osteomyelitis. Sarcomatous changes have a rapid onset and should otherwise not be difficult to differentiate from the luetic involvement. Leukemia produces a predominantly osteolytic destruction. Metastatic lesions, comparable in extent to the luetic involvement, are accompanied by a rapid collapse of the vertebral body and the nature of the process is frequently brought to light by the discovery of the primary lesion.—*J. Zausner, M.D.*

Garfield, J. S. Is radiological examination of the twisted ankle necessary? *Lancet*, Nov. 26, 1960, *2*, 1167–1169. (From: Casualty Department, St. Mary's Hospital, London W.2, England.)

This study was undertaken to assess the value of roentgenographic examination in determining the treatment of injuries of the ankle, and to define the indications for such examination. One hundred and eleven patients with twisting injuries of one ankle were seen by the author in the casualty department of St. Mary's Hospital, London, within twenty-four hours of injury. Roentgenograms of the ankle in neutral position were taken in anteroposterior and lateral projections. The author found that three groups of injuries could be defined: (1) major fractures; (2) minor fractures, such as fractures of the base of the fifth metatarsal or avulsion of cortical flakes from the malleoli, talus, navicular or cuboid. The results of treating such injuries by strapping only were in no case worse than those treated by immobilization in plaster; (3) ligamentous injury without bone damage. All cases in this group were treated simply by strapping.

Ten of the patients were unable to walk after injury and only 2 of these had major fractures. The other 6 patients with major fractures were able to walk. Thus disability is no guide to the likelihood of major fracture.

The severity of pain did not correlate with the presence of a major fracture. Only near the base of the fifth metatarsal did severity and site of pain suggest a specific minor fracture.

In the absence of tenderness, it can be said with certainty that a fracture is not present; in this series those patients with the most tenderness over bony parts and soft tissues had no major fracture. Tenderness over soft tissues rather than over bony points does not exclude a major fracture. Only in the case of fracture of the base of the fifth metatarsal was localization of maximal tenderness any sure guide to the site of fracture.

The author also found that the absence of bruising did not exclude a major fracture, nor was bruising more severe in those patients with major fractures.

All major fractures were associated with swelling and, therefore, the author concludes that it is probably safe to say that in the absence of swelling a major fracture is not present.

Patients with major fractures did not have more limitation of motion than those with purely soft tissue injury. Clinically, the absence of any swelling is a firm indication of the absence of any significant bone or ligamentous damage regardless of the circumstances of injury.

Tenderness localized to the base of the fifth metatarsal is a sure indication of fracture in this site only.

The absence of moderate tenderness, bruising or swelling in a patient under sixty-one years of age who injures the ankle while walking is a good indication that there is no major bone injury. In the remaining cases the clinical features give only an inaccurate guide to the nature of the injury, and in these cases roentgenographic examination is necessary.—*C. Peter Truog, M.D.*

Heuck, F., and Schmidt, E. Die quantitative Bestimmung des Mineralgehaltes der Knochen aus dem Röntgenbild. (The quantitative determination of the mineral content of bones from roentgenograms.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Nov., 1960, *93*, 523–554. (Address: Medizin. Univ.-Klinik, Röntgenabteilung, Kiel, Germany.)

Attempts to determine changes in the mineral content of bones by roentgenography have been made, but no successful method has been established. The authors believe that they have developed such

a method. It is clinically satisfactory when compared with chemical determination. The roentgenologic method is effective with a ±10 per cent methodical error.

A reference system has to be established which allows comparison of long bone with a wedge of established density values. The authors have constructed a step system of such values, consisting of blocks of hydroxyl apatite and a plastic material. Its chemical composition is very similar to that of bone and the apatite is distributed in the plastic material similar in size to the trabeculae. The physical behavior to roentgen rays is similar to that in bone. Experimental data are presented to prove these contentions. There is definite influence of soft tissue density on bone density and the densities of the wedge. In order to minimize these differences, the wedge is placed under the soft tissue close to the bone. The proximal end of the femur is used.

In practice, a good roentgenogram must then be evaluated by means of a photometer. Technically, it has to fulfill certain physical requirements which are listed in detail in the article. The density values are plotted against the density values of the established reference system.

Some clinical findings in normal and abnormal bones are discussed.—*H. W. Hefke, M.D.*

Du Berger, R. L., Masson, G., and Sylvestre, J. Milkman's syndrome—five cases of severe osteomalacia following gastric surgery. *J. Canad. A. Radiologists*, Sept., 1960, *11*, 57–66. (From: Hôpital Général St-Vincent de Paul, Sherbrooke, Quebec, Canada.)

Milkman's syndrome, comprising osteomalacia with spontaneous and symmetric fractures of bone and abortive attempts at repair by nonossified callus, is a rarely reported sequel to postgastrectomy malfunction. The authors report 5 cases encountered between the years 1955 and 1959.

It is known experimentally that, after gastrectomy, adolescent dogs will consistently show a severe degree of osteomalacia, whereas adult dogs are not usually so affected. On this basis one may assume that, if the postgastrectomy Milkman's syndrome is uncommon in man, it is partly because gastric surgery is usually done in patients well past the growth period. All the patients in the authors' series were in early adult life, the age at operation ranging from twenty-three years to thirty-four years. The interval between surgery and the onset of symptoms attributable to bone disease was approximately two to four years, with varying degrees of the dumping syndrome occurring during the interval.

A commonly accepted theory to explain the dumping syndrome is based on the osmotic attraction of interstitial fluids into the jejunum by a small bowel bolus of high osmolarity, with a resultant state of mild shock caused by lowered blood plasma volume. Recently, however, it has been shown that osmotic imbalance can be demonstrated in completely asymptomatic patients and the only distinctive feature between symptomatic and asymptomatic cases is the existence of increased renal blood flow in those with symptoms. Thus, it seems unlikely that a single roentgen examination would predict the extent and severity of malabsorption or determine whether the dumping syndrome is symptom-producing or not.

The cases reported illustrate that no clear connection can be shown between the severity of the dumping syndrome and the degree of osteomalacia. One patient presented with complaints of lumbar, thoracic and pelvic pain in the absence of gastrointestinal or dumping symptoms. In 2 patients, determinations of blood plasma volume and blood glucose and potassium levels were made simultaneously with the roentgen examination after the patient had ingested 2 ounces of barium in 150 cc. of 50 per cent glucose solution. A depression of serum potassium and a 25 per cent decrease in blood plasma volume coincided with the roentgenographic finding of dilatation of the jejunum and edema of the mucosal folds. One patient experienced corresponding symptomatology, but the other was asymptomatic.

It is concluded that the dumping syndrome and secondary osteomalacia as sequel of gastrectomy are more likely to occur in the young individual and that caution should be used in the evaluation and selection of young ulcer patients for gastrectomy.—*Leslie K. Sycamore, M.D.*

Richards, A. J. Non-tuberculous pyogenic osteomyelitis of spine. *J. Canad. A. Radiologists*, Sept., 1960, *11*, 45–49. (From: Regina Hospital, Regina, Saskatchewan, Canada.)

Pyogenic osteomyelitis of the spine has been diagnosed more commonly in recent years than previously, probably due to a greater awareness on the part of both clinicians and radiologists which, in turn, stems from the decreased incidence of tuberculosis and the realization that in the past many cases of osteomyelitis have been misdiagnosed as tuberculosis.

Any of the common pathogens may be the infecting organism, but the majority of cases are due to a Staphylococcus; typhoid, paratyphoid and Brucella infections occasionally occur.

Batson's demonstration of the extensive anastomoses of the veins of the vertebral column with those of the thoracic, abdominal, and pelvic cavities explains the mechanism for metastatic involvement of the spine from infections elsewhere. The focus follows the usual course of an inflammatory process with eventual destruction of bone and frequently some degree of collapse of the involved vertebra. If the destruction is peripheral, there may be corresponding wedging of the vertebral body. The intervertebral

disk may herniate into an area of destruction situated on the intervertebral margin. The neural arch may be involved and destruction of the pedicle may result in forward or lateral slipping of the vertebra. Rupture may occur into the neural canal with resultant epidural abscess. The adjacent disk is usually involved by direct extension. Soft tissue extension is not as common a feature as it is in tuberculosis. Osteoblastic reaction to the infection occurs early and is a prominent feature.

The author reports a series of 10 patients with 11 lesions, 2 of the lesions occurring in the same patient at different levels. The majority of cases was in the lumbar spine. Roentgenologically, thinning of the intervertebral disk was the earliest and most reliable sign of the disease, except in 1 case involving the central portion of the vertebral body. In the early phase this was associated with a loss of definition of the adjacent superior or inferior surface of the involved vertebral body. Involvement of the neural arch was demonstrated three times. The degree of bone destruction and collapse varied, but in no case was it as extensive as is commonly seen in tuberculosis. Osteoblastic response was consistently present in a matter of weeks and fusion between adjacent bodies resulted in several cases.

The source of infection was presumed to be from the lower urinary tract in 2 cases, from the ear in 1 and from a perinephric abscess in 1. No source could be determined in the other 7.

The differential diagnosis is primarily between tuberculous and pyogenic infection and the following table is offered as an aid:

Tuberculous	*Pyogenic*
No osteoblastic response	Marked osteoblastic response
Large paravertebral abscess	Small or no paravertebral abscess
Marked rarefaction	Less rarefaction
Slow course	More rapid course
Marked destruction and collapse	Less destruction and collapse

—*Leslie K. Sycamore, M.D.*

Giedion, A. Weichteilveränderungen und radiologische Frühdiagnose der akuten Osteomyelitis im Kindesalter. (Soft tissue changes and early radiologic diagnosis of acute osteomyelitis in childhood.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1960, *93*, 455–466. (Address: Steinviesstr. 75, Zürich, Switzerland.)

Visible bone changes are known to be a late manifestation of acute osteomyelitis. An interval of ten to fourteen days after onset of symptoms usually is required for osseous and periosteal lesions to be recognized roentgenologically. Therefore, one has to depend on clinical findings.

Early symptoms are malaise, fever, and migrating joint pains. Localized signs are circumscribed pain, swelling, limping, and guarding of the involved extremity. Occasionally, a history of trauma can be elicited.

Relatively few cases are recognized early in infants because of inability to localize a lesion. Of a total of 23 patients, only 5 were below the age of five, 6 children were between five and ten years old, and 12 between ten and sixteen years. The distal femur was affected 7 times, the proximal tibia 6 times, and the proximal humerus and distal tibia 3 times, each. The proximal femur, distal humerus, distal fibula, and calcaneus, respectively, were the sites in the 4 remaining cases.

Most of the patients were given antibiotics within the first week of illness, although no definite diagnosis had been established. This accounts for an atypical course and delay of visible bone changes for three weeks and more.

Therefore, early roentgen signs in the soft tissues have to be more and more relied upon. These are disappearance of fat spaces near end joint and swelling of nearby muscles. Finally, the subcutaneous layers become obliterated and a massive edema develops. Comparative views of the normal opposite side are very helpful. Of significance is also an extension of the process from the inside in outward direction, in contrast to skin infections which only spread superficially. Diagnostically important is a metaphyseal location and a normal adjacent joint. These findings eliminate confusion with septic arthritis.

Five cases are briefly reported and well illustrated. Most of these were not correctly diagnosed or treated until the classic soft tissue changes suggested an early phase of acute osteomyelitis.—*Ernest Kraft, M.D.*

Rabaiotti, A., Rossi, L., Schittone, N., and Gandini, G. E. Le alterazioni vascolari nell 'artropatia tabetica. (Vascular changes in tabetic arthropathy.) *Ann. radiol. diag.*, 1960, *33*, 115–121. (From: Istituto di Radiologia dell 'Università e degli Ospedali Riuniti de Parma, Italy.)

The authors studied 2 cases of tabetic joints by using angiography. They demonstrated increased arterial and capillary vascularity of the joint capsule. These studies also showed increased venous drainage and flow. In many respects, this increase in vascularity is not unlike that found in certain malignant neoplasms, in that it is accelerated and disorganized.

The findings attest to the neurotrophic and vasomotortrophic changes of the tabetic joint rather than to primary vascular changes, which would reduce the vascular bed and nutrition to the joint capsule.—*Peter E. Russo, M.D.*

Blood and Lymph System

Hallerbach, H., and Luster, G. Experimentelle und klinische Erfahrungen mit der Hochdruckinjektionsspritze nach Gidlund für die selektive Angiokardiographie. (Experimental and clinical experiences with Gidlund's high pressure injector syringe for selective angiocardiography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Nov., 1960, *93*, 565–582. (Address: H. Hallerbach, Strahlenklinik Prof. Janker, Baumschul-Allee 12/14, Bonn, Germany.)

Since selective angiocardiography is an advance over intravenous cardiography, its technical factors are being improved. One of them is the high pressure injector syringe devised by Gidlund. In order to achieve a high pressure in the long, narrow catheter, the glass injector was replaced by a metal one. By using a compressed air cylinder, the contrast material can be accurately controlled as to injection pressure and speed of flow of the injected material. The amount of contrast medium can be predetermined and controlled, and the temperature of the solution can be maintained at the desired degree.

The apparatus, which is manufactured in Stockholm, was tested and the experimental findings of injection pressure, speed, flow of solution, viscosity of solution, etc., should be read in the original article, which contains many charts and statistical data.

The clinical use of the apparatus is also considered and many practical suggestions are offered. A considerable number of reproductions of angiocardiograms illustrates the clinical findings. The injection factors must be individualized as suggested by anatomic and hemodynamic differences in different anomalies. Incorrect positioning of the tip of the catheter is still a danger since it may produce myocardial damage.

It is the opinion of the authors that the Gidlund injector is a valuable aid for selective angiocardiography.—*H. W. Hefke, M.D.*

Thurn, P., Schaede, A., Hilger, H. H., and Düx, A. Zur perkutanen, retrograden, thorakalen Aorto- und Laevokardiographie. (Retrograde percutaneous thoracic aortography and levocardiography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1960, *93*, 393–418. (From: Medizinische Klinik der Universität, Bonn, Germany.)

In recent years, percutaneous retrograde aortography has been developed into a routine procedure thus making possible selective visualization of the aorta with its branches and of the left heart chambers. The authors have successfully used the method in 68 consecutive cases.

The procedure is done under general anesthesia with preliminary sedation. A femoral artery is punctured percutaneously. A thin catheter is introduced and is led upward to the base of the aorta. Passage into the left ventricle can be easily accomplished except in extreme stenosis of the aortic valve. The right brachial artery may have to be used instead of a femoral artery in far advanced coarctation of the thoracic aorta. Pressure readings are done in the left ventricle and aorta, to be followed by rapid injection of renografin (76 per cent). The adult dose is 50 cc. in aortography and 60 to 70 cc. in levocardiography. After completion of the study and withdrawal of the catheter, manual compression of the femoral artery is required for ten to fifteen minutes. It is emphasized that continuous electrocardiographic tracings must be done throughout the procedure.

Indications for aortography are (1) patent ductus arteriosus, (2) obliteration of the subclavian artery, (3) anomalies of the aortic arch and of cervical arteries, (4) aortic isthmus stenosis, (5) aneurysm of the sinus Valsalvae with and without perforation into a chamber and other types of aneurysm, (6) anomalous orifices of coronaries and fistulae between a coronary and a chamber or the pulmonary artery, and (7) aimed coronography in coronary disease.

Indications for levocardiography are (1) aortic stenosis (valvular, subvalvular, and supravalvular), (2) idiopathic hypertrophy, Bernheim syndrome, endocardial fibroelastosis, tumor, and constrictive pericarditis, (3) aortic insufficiency, especially in high septal defect, (4) mitral insufficiency, (5) combined mitral aortic lesions, especially preoperatively in mitral stenosis, (6) ventricular septal defect with left-to-right shunt for preoperative localization of defect, and (7) transposition of the great vessels.

Fifteen different conditions are illustrated with roentgenograms, electrocardiograms and pressure curves. The differential diagnosis of aortic stenosis, mitral insufficiency, and ventricular septal defect is discussed in detail, and it is stressed that proper evaluation of reflux from the left ventricle into the dilated left atrium requires continuous electocardiographic monitoring throughout the levocardiography. —*Ernest Kraft, M.D.*

General

Lusted, Lee B. Logical analysis in roentgen diagnosis; Memorial Fund lecture. *Radiology*, Feb., 1960, *74*, 178–193. (Address: Department of Radiology, Strong Memorial Hospital, Rochester 20, N. Y.)

The complete, logical analysis of a roentgen examination may be divided into four parts: (a) film exposure and processing techniques which produce optimum usable information; (b) visual physiology of film viewing; (c) psychologic factors; (d) system-

atic decision-making, the process of diagnosing. Accurate roentgen diagnosis requires first, that the data be accurate; second, that the evaluation of the data be thorough and complete; third, that the interpretation of the data by systematic.

Systematization of the reasoning processes helps the radiologist to increase his diagnostic accuracy. Since the reasoning processes are susceptible to analysis, errors from this source can be eliminated. Certain basic concepts are inherent in any medical diagnostic procedure, even when the physician uses them subconsciously. Symbolic logic and probability contribute to our understanding of the reasoning foundations of roentgen diagnosis, while a third mathematical discipline, value theory, can aid in the choice of an optimum treatment plan.

There are three factors involved in the logical analysis of medical diagnosis: (a) medical knowledge, which relates disease complex to symptom complex, (b) the symptom complex presented by the patient, and (c) the final disease complex diagnosis. Each of these three factors can be expressed in terms of symbolic logic as a Boolean function. Some interesting work is being done on bone tumor analysis by Dr. Gwilym Lodwick who is using a form of digital notation and punch cards. Machine analysis of the punched card data obtained shows promise of a high degree of diagnostic accuracy. It is possible that the system may enable the radiologist to give a most accurate diagnosis and prognosis of a bone tumor from the roentgenogram.

Chance and probability are part of medical knowledge; therefore, probability is part of the diagnosis itself. At the present time very few specific symptom probabilities are known; medical textbooks do not give numerical values. If enough statistics for a certain symptom-disease complex are available, probabilities can be determined and methods can be devised for using these probabilities in diagnosis. Logic and probability concepts may help medical students learn to be more efficient and accurate in medical diagnosis, and may enable radiologists to decrease observer error and increase diagnostic accuracy.—*Arno W. Sommer, M.D.*

Trout, E. Dale, Kelley, John P., and Lucas, Arthur C. Influence of cable length on dose rate and half-value layer in diagnostic x-ray procedures. *Radiology*, Feb., 1960, *74*, 255–264. (Address: E. D. Trout, 4855 Electric Ave., Milwaukee 1, Wis.)

Certain changes in technique and equipment are currently being used in an effort to reduce patient dosage during diagnostic fluoroscopy and roentgenography. These changes are the tendency toward reduced tube current and higher kilovoltage in fluoroscopy and the use of tube-supporting structures requiring longer shock proof cables. The assumption has been made that a reduction in tube current causes a directly proportional reduction in patient dose. This assumption may not be valid at the low currents used in fluoroscopy, since the electrical capacity of shock proof cables acts as a filter, having a tendency to alter the waveform to the roentgen-ray tube in the direction of constant potential. This effect is related to the length of the cable, the tube current, and the kilovoltage used. The authors present a detailed study of these factors and their relationship to patient dose.

The equipment used was a full-wave rectifying unit rated at a maximum voltage of 130 kv. peak and maximum current of 500 ma. Four regular catalogue cables were used with lengths of 15, 24, 30 and 40 feet. The kilovoltage calibration was accomplished by a method, originally proposed by Greening, which consists of determining the machine setting at which the K series fluorescence radiation from a secondary radiator just appears. This method was not the primary objective of this investigation but may well prove to be the most significant contribution. The roentgen-ray output waveform, dose rate, and half value layer were determined with respect to the variables of kilovoltage, tube current, and cable length. For further details in methods and technical factors the original article is recommended.

The authors conclude that dose rate may not be considered linear with tube current in equipment of the type studied. The actual relationship between dose rate and tube current depends on the cable length and kilovoltage. Therefore, the only safe procedure is to take measurements under actual operating conditions.—*Edward B. Best, M.D.*

Amalric, R., Geller, S., Lagarde, C., and Laurens, G. Les gynécomasties; étude de 113 cas.—Données de la radiographie simple du sein. (Gynecomastias; a study of 113 cases. Data on plain roentgenography of the breast.) *Presse méd.*, Oct., 1960, *68*, 1562–1565. (From: Centre régional de Lutte contre le Cancer de Marseille, et Service de Radiologie de l'Hôpital Maritime de Toulon, France.)

Simple roentgenography of the breast in gynecomastia delineates the glandular tissue, which can be classified as dendritic, nodular, or triangular in pattern; it also enables one to differentiate cases of simple adiposity. Statistical analysis of the 113 cases showed two peaks in the incidence of the disease, at puberty and at andropause. Usually bilateral, the lesion is rarely precancerous. In more than half of the cases, the etiology was determined, the common causes being testicular atrophy or tumor, and therapeutic agents, particularly estrogens, isonizide and prednisone.—*Frank A. Riebel, M.D.*

Catinat, J., Auvert, J., Casassus, P., Nezelof, Ch., and Roy, J.-L. (Paris, France.) A propos d'un nouveau cas de syndrome de Budd-Chiari. (On a new case of Budd-Chiari's syndrome.) *Presse méd.*, Oct., 1960, *68*, 1749–1752.

The authors report a classic case of Budd-Chiari's syndrome, or thrombosis of subhepatic veins. Enormous esophageal varices were demonstrated *in vivo*, and postmortem cavography showed the difficulty in refluxing opaque medium into the liver, even under high pressure. Portography, done via the superior mesenteric vein, revealed perfect intrahepatic arborization. Possible medical and surgical treatments are discussed.—*Frank A. Riebel, M.D.*

RADIATION THERAPY

Vaeth, Jerome M. Nasopharyngeal malignant tumors: 82 consecutive patients treated in a period of twenty-two years. *Radiology*, Mar., 1960, *74*, 364–372. (Address: Department of Radiology, University of California Medical Center, San Francisco 22, Calif.)

The results of a study of 82 consecutive cases of malignant nasopharyngeal tumors are reported. These patients were treated from 1932 to 1954 in the Department of Radiology of the University of California, San Francisco. This represents 24 per cent of 3,353 treated cancer cases and 13.3 per cent of 614 head and neck tumors. Fifty-eight patients in the series were men and 24 were women. Enlarged cervical lymph nodes were found unilaterally in 34 patients and bilaterally in 25. Cervical lymphadenopathy was the initial and only complaint in 24 patients. Symptoms and signs related to the ears or to the nose occurred next in frequency. Cranial nerve involvement was present in 19 patients; the cranial nerves most commonly involved were the fifth and sixth. Nine patients (11 per cent) had erosion or invasion of the base of the skull. The average duration of symptoms and signs was about eight months. Frequently, incorrect diagnosis or mismanagement preceded recognition of the tumor. Epidermoid type tumors occurred in 47 patients; next in order were lymphoepitheliomas (30.5 per cent), lymphosarcomas (4.9 per cent) and adenocarcinomas (2.4 per cent).

Treatment, in general, consisted of local irradiation of the nasopharyngeal tumor and immediate lymphatic drainage areas, intracavitary radium, cobalt 60, or a combination of external and intracavitary irradiation. Thirty-one of the 82 patients received 1 mev. external irradiation, either alone or supplemented by intraoral cone therapy, intracavitary radium, or cobalt 60 to the primary lesion. Cervical lymph node areas were treated with irradiation in the medium voltage range. The remaining 51 patients were treated at 400 kv. or 200 kv. supplemented by intraoral cone, intracavitary cobalt 60 or intracavitary radium. A few patients were treated solely by intracavitary cobalt 60 to the primary lesion.

The average survival was twenty-five months. Twenty-three (28.2 per cent) of the 82 patients survived five or more years. Six patients have survived more than ten years. Lymphosarcoma appeared to have the best prognosis.—*Arno W. Sommer, M.D.*

Rübe, W., and Flöte, F. Osteoradionekrose der Mandibula. (Osteoradionecrosis of the mandible.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1960, *93*, 472–482. (Address: Strahleninstitut der FU Berlin, Spandauer Damm 130, Berlin-Charlottenburg, Germany.)

The authors report their experience with radionecrosis of the mandible from 1950 until 1957. During this period 192 tumors of the oral cavity were observed. Fifteen cases (7.8 per cent) developed mandibular necrosis. Of these, 7 were treated with roentgen rays alone and the remaining 8 with interstitial radium, followed by roentgen rays.

There was definite increase of the complication as larger doses of ionizing rays were applied more and more frequently. Other factors were caries of the teeth which stimulated mucosal ulceration and infection of the underlying mandible. This resulted in necrosis and sequestration of bone. Also responsible were continuous trauma from the chewing process and drying of the mucosa which eliminated the protective effect of the saliva.

Osseous necrosis became manifest as early as eight months following radiation therapy and in others as late as nine years afterward. The roentgenographic signs usually are preceded by long-standing soft tissue swelling and subsequent ulcerations of the oral mucosa. Roentgen findings in the early phase are osteoporosis and irregular contour of the mandible. This is followed by destructive changes from the alveolar ridge downward, osteolysis with debris, and finally pathologic fracture with sequestration.

The most effective treatment is prophylactic. High voltage currents are preferred nowadays as they cause less bone destruction than low voltage currents. Another preventive measure is insertion of radium needles at an angle instead of parallel to the mandible. Hygiene of the mouth must be carefully observed, and remaining teeth have to be extracted, with penicillin prophylaxis several weeks prior to radiation therapy. Occasionally, extraction may have to be postponed until after completion of treatments.

Therapy of mandibular necrosis does not depend on roentgen findings or the presence of ulcers. Local and general antibiotic measures as well as washing will expedite the cure of ulcers and fistulae. Sequestra usually protrude spontaneously. The mucosa heals

promptly in spite of underlying osseous necrosis and pathologic fractures. Sequestrectomy, with the aid of antibiotics, modern anesthesia, and blood transfusion, has become the method of choice, as it expedites healing and prevents development of fistulae and ulcers. A well-fitting and functioning prosthesis is now possible in advanced cases, even when bone has been resected.

Numerous photographs and roentgenograms illustrate this interesting article.—*Ernest Kraft, M.D.*

Voltz, P. W., Jr., Mallams, J. T., and Swindell, G. E. Radium attenuation in treatment of carcinoma of cervix. *South. M. J.*, Oct., 1960, *53*, 1205–1210. (From: Sammons' Irradiation and Nuclear Medicine Department, Baylor University Hospital, and the Department of Radiology, Southwestern Medical School, Dallas, Texas.)

The Manchester method is a well-known technique for treating carcinoma of the cervix with radium applicators that consist of thin uterine tubes and ovoids of varying sizes. A loading system is used that varies in a simple number of units to keep the dosage rate fairly constant to a fixed point A in the paracervical triangle.

Fletcher and his associates developed rigid applicators with scissor-like handles that extend outside the introitus and facilitate the insertion of the applicators and maintain them in position. The Fletcher ovoids with the recommended loadings permit an increase in the dose rate to the lateral pelvic wall without increasing the dose to point A. Fletcher based his dosage techniques on the Manchester method as his ovoids gave only 5 per cent less than the Manchester ovoids. The Fletcher ovoids were loaded with 15, 20 and 25 mg. of radium, respectively, for the small, medium and large ovoids. The dosage rate with these loadings varied as much as 25 per cent from the ovoids to point A with 1 cm. separation.

The authors used Mallory 1,000 metal as an attenuator in order to reduce the dosage rate from the 25 mg. radium tubes. Mallory metal is an alloy of 90 per cent tungsten, 6 per cent nickel, and 4 per cent copper. It is hard and machines easily, is 1½ times as dense as lead, and is noncorrosive. The large Fletcher ovoids do not require an attenuator. Attenuators of different thicknesses were used for the medium and small sized ovoids to reduce the dosage rate to the radium equivalents given with the Manchester technique. The dose delivered within the cervical triangle using this method falls within the optimum dosage range when the standard times of the Manchester method are used with radium alone or with combined therapy.

The Fletcher applicators, the Mallory attenuators, the four sizes of tandems and 95 mg. of radium permit all standard and satisfactory nonstandard radium applications for treatment of carcinoma of the cervix. The amount of radium used is 40 per cent less than that required using the Fletcher applicators alone.—*Charles W. Cooley, M.D.*

Egan, Robert, and Johnson, Gordon C. Multisection transverse tomography in radium implant calculations. *Radiology*, Mar., 1960, *74*, 407–413. (Address: R. Egan, University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston 25, Texas.)

The authors describe the use of multisection transverse laminagraphy as an aid in certain radium implant calculations, particularly those about the head and neck. With standard radium distributions, or limited deviation from the standard, roentgenograms in two planes will usually outline the completed implant and are adequate for calculation purposes. For more marked deviations and for multiple or curved plane and volume implants, the identification of needles on plain roentgenograms is difficult. The perpendicular projection technique and stereoroentgenograms are often of help in such cases. As an additional reconstructive aid, the authors have applied multisection transverse laminagraphy in these difficult cases. Conventional laminagraphy with linear tube travel is not as satisfactory since the axis of implants frequently parallels the axis of the body.

Certain modifications were applied to a Siemens Transversal Planigraph to improve diagnostic detail and facilitate clinical application. These include increasing and fixing the tube stand-patient distance, limiting the vertical tube travel, and replacing air compression bags by foam rubber pads. A plastic head rest was devised along with a multiple cassette box. The method described is now in regular clinical use as an aid in dosage calculation of radium implants about the head and neck. The authors feel that it allows rapid and accurate identification of radium needles and their relationships, improves the control of radiation dosage, and provides three dimensional insight into the clinical use of interstitial radium.—*Edward B. Best, M.D.*

Graham, John B., Graham, Ruth M., Sotto, Luciano S. J., and Baily, Norman A. Spent radon seeds: I. Late effects. *Radiology*, Mar., 1960, *74*, 399–402. (From: Roswell Park Memorial Institute, Buffalo, N. Y.)

The authors present evidence that spent radon seeds, long regarded as being inert, may actually continue to emit measurable irradiation for many years. Radon degenerates into radium C, D, and E, all radioactive. Radium D has a half-life of nineteen years but, as its radioactivity consists mainly of alpha or beta radiation, it has been assumed that this did not escape its gold sheath. In recent months,

5 cases of late recurrence or of complications following radon seed implantation for carcinoma of the cervix have been seen by the authors. All of these cases had detectable radiation from the retained seeds. A determination of the spectrum of radiation from these seeds revealed that beta rays of 1.17 mev. emitted by radium E striking the gold sheath created a continuous spectrum of x-radiation with peaks at 70 kev. and 167 kev. These x-rays are of low intensity, but, acting on previously irradiated tissue and acting continuously over a long period of time, some biologic effect would be anticipated, either destructive or carcinogenic. Cytologic examinations of patients treated with radon seeds as compared with those treated by radium and roentgen rays apparently substantiated this.—*John S. Alexander, M.D.*

Johns, H. E., and Skarsgard, L. D. Spent radon seeds: II. Radiation from spent radon seeds. *Radiology*, Mar., 1960, *74*, 403–406. (Address: H. E. Johns, Department of Physics, University of Toronto, Toronto, Ontario, Canada.)

The authors review the decay scheme of radon and calculate the theoretic exposure dose obtained 1 cm. from a 1 mc source of radon as 0.37 r/year. Five spent radon seeds, each with an initial activity of 1.13 mc on September 16, 1933, were taken from a patient and measured in December, 1958, utilizing a sodium iodide crystal at a distance of 8.2 cm. The figure obtained after corrections for decay of radium D over a twenty-five year period was 76.5 μr/hr. at 1 cm. per initial mc, which was considered consistent with the calculated exposure dose above. The exposure dose rate of the spent radon seeds per initial mc at 1 cm. in μr per hour and the mean and maximum absorbed doses for each patient were then calculated. Examination of these figures revealed that the absorbed doses ranged from 100 to 300 rads over a ten to twenty year period for these patients. While this dose is admittedly small, the authors feel that the possibility of its causing chronic irritation cannot be completely ruled out.—*John S. Alexander, M.D.*

Chilko, Alexander J. Contribution to problem of diagnosis, treatment and prognosis of Wilms' tumor. *J. Urol.*, June, 1960, *83*, 804–812. (Address: 1040 Park Avenue, New York 28, New York.)

Three types of Wilms' tumors have been described. The most common one starts in the kidney parenchyma and is enclosed in a connective tissue capsule which separates the tumor tissue from the normal kidney parenchyma. The second type begins in the kidney proper and infiltrates the kidney parenchyma without a definite capsule. The third type of tumor originates in the "renal anlage" and is extracapsular and retroperitoneal.

The biologic behavior and radiosensitivity of Wilms' tumors vary depending upon the relative number of anaplastic cells to epithelial cells. The host resistance is another unknown factor, at present.

The therapy of Wilms' tumor consists of the use of surgery or irradiation or combinations of the two. In reports covering large series of cases by Harvey and Scott, the best over-all results were obtained by nephrectomy with preoperative and postoperative roentgen treatments.

The author reports 2 cases of Wilms' tumors treated by irradiation. Since the tumors consisted of radioresistant and radiosensitive elements, the treatment plan utilized small single doses to destroy the radiosensitive cells. This method reduced the toxic effects (created by the absorption of destroyed cells) on the parenchyma of the normal kidney and other organs and avoided serious skin erythema. A large total dose was thus employed to destroy or inhibit the radioresistant portions of the tumor.

The method of treatment resulted in a large tumor dose delivered through two or three fields in small single doses over a period of from one to two years. An alternate plan consisted of therapy to one area daily until a total dose of 1,000 r (air) per area was reached. After two days of rest, a second total dose of 1,000 r (air) per area was given. Then following the same routine, three, four, five, and six day intervals were allowed between the 1,000 r increments to each area until a total air dose of from 3,000 to 5,000 r had been administered to each field. The patients were kept in bed under strict supervision during the first month. Palpation of the abdomen was limited to the minimum. These patients were studied by excretory pyelography because of possible trauma and metastasis which could result from retrograde pyelography. The author believes that this might have accounted for the absence of metastases in his 2 patients.

The first case was that of a fourteen month old boy with a Wilms' tumor involving the right kidney, which was considered inoperable. This patient was treated with the following factors: 200 kvp.; 5 ma.; focal distance, 40 cm.; filters of from 0.5 to 1.0 mm. Cu with secondary filter; half value layer, 0.9 to 1.4 mm. Cu; total air dose, 5,000 r to each of two areas; estimated total tumor dose, 7,110 r; fields, 15 by 15 cm. at the beginning with a reduction in size to correspond to the size of the tumor. From August, 1934 to June, 1936, 122 treatments were administered. Therapy was started with 115.8 r (air) per area with 0.5 mm. Cu filter until a total air dose of 1,000 r (tumor dose, 1,420 r) was reached. The filter was then increased to 1.0 mm. Cu and the dose was reduced to 76.2 r (air) per area.

In this first case the size of the kidney returned to normal by the end of the third month. The patient remained well until 1946, when hematuria developed

and a right nephrectomy was performed. The pathologic examination showed no recognizable kidney tissue but cystic areas containing tumor cells surrounded by a sclerosed renal capsule were present. At the time of this report the patient was twenty-six years of age and well. There was no demonstrable evidence of skin damage.

The second case was that of a four and one-half year old girl with a tumor of the right kidney (considered to be a possible embryonal adenosarcoma), who was treated by radiation therapy only. The plan of therapy employed for the first patient was modified as follows: the filter was increased to 1.0 mm. Cu (half value layer of 1.4 mm. Cu), and later to 2.0 mm. Cu (half value layer of 1.9 mm. Cu); the focal distance was 50 cm.; the dose per area the first month was 135 r (air) and afterwards 90 r (air); a lateral field was added. A total of 85 treatments was delivered in fourteen months. The total dose in air was 3,000 r to each of three ports. The total tumor dose was 6,334 r.

In this second case, eleven years after therapy was completed the right kidney was removed. The pathologic examination revealed no tumor tissue but distortion of the architectural pattern of the kidney due to irradiation was noted.—*J. N. Ané, M.D.*

Conti, Eugene A., Patton, George D., Conti, Jane E., and Hempelmann, Louis H. Present health of children given x-ray treatment to the anterior mediastinum in infancy. *Radiology*, Mar., 1960, *74*, 386–391. (Address: L. H. Hempelmann, 260 Crittenden Blvd., Rochester 20, N. Y.)

The purpose of the present study was to obtain further information concerning the incidence of malignant disease in children given roentgen treatment to the anterior mediastinum in infancy. A survey was made of 1,564 children in Pittsburgh who had been given roentgen treatment to the thymus gland between 1938 and 1946. The diagnosis of thymic enlargement had been made in 224 of these cases at birth. Of these, 80 per cent were treated with 200 to 450 r of 140 kv. peak roentgen rays through a 4×4 cm. port. Of the 1,340 children with thymus glands of normal size, 95 per cent were given 150 r using the same treatment factors. Between 1956 and 1958, the families of 89.6 per cent of the treated children were questioned about the medical histories of these children and of their 2,923 untreated siblings. The death records of the Pennsylvania State Department of Health were also searched, as were the leukemia records from 1954 to 1957.

No cases of malignant disease were found in the treated group, although 4 cases of cancer, including 1 of leukemia, would be expected to occur in a group of children of this size and age distribution. The 4 malignant tumors in the sibling group, including 1 case of leukemia, compared closely with the expected number.

Because of the method of study and the absence of definitive information for 10 per cent of the treated children, the incidence of neoplasia in this group can be compared with that in the general population only with certain reservations. Nevertheless, it seems likely that the cancer and leukemia incidence in the treated children is not greatly increased over the expected incidence. It is suggested that the small port size (4×4 cm.) used in treating these children could explain the difference in incidence of neoplasia in this group of children and in those previously studied.—*Walter H. Jarvis, Jr., M.D.*

RADIOISOTOPES

Koutras, D. A., Alexander, W. D., Buchanan, W. W., Crooks, J., and Wayne, E. J. Stable iodine metabolism in non-toxic goitre. *Lancet*, Oct. 8, 1960, *2*, 784–786. (From: University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, W.1, Scotland.)

Nontoxic goiter occurs both endemically and sporadically. The endemic form is a result of iodine deficiency. The etiology of sporadic nontoxic goiter is controversial and some of the suggested causes are: contaminated water supply, virus and other infections, goitrogens, excess calcium in the diet, iodine deficiency, and dyshormonogenesis.

Evidence of iodine deficiency in endemic goiter is indicated by the elevated uptake of radioiodine associated with a normal level of plasma protein bound radioiodine, a normal level of protein bound iodine (P.B.I.) and a low daily urinary iodine excretion. The plasma inorganic iodine (P.I.I.) is important in determining the absolute iodine uptake by the thyroid gland in order to show whether the high uptake of radioiodine is the result of iodine deficiency with a rapid turnover of available iodine or an incapacity of the gland to completely synthesize the normal amount of circulating iodine. Iodine deficiency is clearly present if low P.I.I. levels are found.

Twenty-one cases of sporadic goiter not due to any known cause in an area known to be free from endemic goiter were studied using the above tests. A comparison was made with a control group of 13 cases without goiter and without evidence of thyroid disease and in an area where iodized salt was rarely used. I^{132} was used in 28 cases and I^{131} in 6 cases. The results showed that the radioactive iodine uptake in the goiter group was higher (mean 39.9 per cent) than in the control group (mean 25.6 per cent). The mean thyroid clearance in the goiter group was 61.1 ml. per minute as compared with 23.0 ml. per minute in the control group. The plasma inorganic iodine in the goiter group was 0.02 to 0.09

μg. per 100 ml., whereas the lowest in the control group was 0.10 μg. per 100 ml. The absolute iodine uptake of the goiter group was slightly lower than that of the normal group, but not significantly so. The mean protein bound iodine was the same in both groups. The twenty-four hour urinary iodine excretion was low in the goiter group as compared with the control group. The renal clearance of the radioiodine was slightly but not significantly higher in the goiter group.

The intrathyroid exchangeable iodine studies suggest that goiters contain a normal amount of iodine in an increased tissue mass.

Cases with low plasma inorganic iodine have a high thyroid clearance rate of radioiodine that acts as a compensatory mechanism which maintains the absolute uptake of the thyroid gland within a normal level.

The authors conclude that the etiology of nontoxic goiter is complex and that iodine deficiency is probably a causative factor of sporadic goiter.—*Charles W. Cooley, M.D.*

Pimparkar, B. D., Tulsky, E. G., Kalser, M. H., and Bockus, H. L. Correlation of radioactive and chemical faecal fat in different malabsorption syndromes. *Brit. M. J.*, Sept. 24, 1960, *2*, 894–900. (Address: B. D. Pimparkar, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.)

The most accurate method of quantitatively determining faulty assimilation of fat is a balanced technique accurately calculating the components in digested food and chemically determining the residue of the stools. This method is prohibitive in the smaller hospitals. The I^{131} labeled fatty absorption tests are easier to do and may be carried out in any radioisotope laboratory.

One hundred and two patients from the Gastrointestinal Service of the Graduate Hospital of the University of Pennsylvania who were suspected of having malabsorption and 24 normal cases were studied to determine the accuracy of radioactive I^{131} labeled triolein studies as compared with the fecal chemical intake-excretion studies as a diagnostic aid in the various malabsorption syndromes. All of the cases received a standard diet and were given Lugol's solution for two days to block the thyroid gland. The I^{131} triolein meal was prepared in both emulsion and capsule form and was administered to the fasting patients about one or two hours after the first dose of carmine was given. Blood was drawn every two hours until a peak of radioactivity was determined. Stools were collected until the last specimen did not show significant radioactivity.

Blood peak radioactivity, fecal radioactivity and fecal chemical fat were determined for the group. The mean blood peak radioactivity in 24 normal cases was 19 ± 5 per cent of the administered dose. The mean fecal radioactivity in 20 normal cases was 3 ± 1.94 per cent gm. per day of the administered dose. The mean fecal chemical fat in the same group was 4 ± 1.6 gm. per day. Generally, in each group that had abnormal fecal chemical fat, the fecal radioactivity test was abnormal in about 75 per cent of the cases, while the blood peak radioactivity was abnormal in about 50 per cent. Of those who had normal fecal chemical fat, nearly 80 per cent had a normal fecal radioactivity and the blood radioactivity was normal in nearly 85 per cent. The fecal radioactivity determination was a better index for the presence of steatorrhea than the blood radioactivity, but the accuracy increased when both the studies were done. The patient's chance of being normal was about 85 per cent to 95 per cent if both the blood peak radioactivity and the fecal radioactivity values were normal; but if both values were abnormal, the chance of his having steatorrhea was about 75 per cent.

The authors recommend that, if blood peak radioactivity and fecal radioactivity are abnormal, the patient should have fecal chemical balance studies to establish the diagnosis definitely and to quantitatively estimate the steatorrhea.—*Charles W. Cooley, M.D.*

MISCELLANEOUS

Finkel, Miriam P., Bergstrand, Patricia J., and Biskis, Birute O. The consequences of the continuous ingestion of Sr^{90} by mice. *Radiology*, Mar., 1960, *74*, 458–467. (Address: M. P. Finkel, Argonne National Laboratory, P. O. Box 299, Lemont, Ill.)

In order to provide some direct information bearing on the consequences of various levels of radioactive dietary contamination, mice are being maintained on food containing Sr^{90}. The present report is an interim rather than a final evaluation of the data, since many of the experimental animals are still alive.

Two groups of mice are being maintained on food containing Sr^{90}. The first was placed on the special diet at 110 to 250 days of age, and this group produced the second, which has been exposed to Sr^{90} since conception. Levels of dietary Sr^{90} as high as 10 μc/gm. Ca did not adversely affect conception, parturition, or lactation. The median survival time of the dams maintained on this level of Sr^{90} for 525 days was reduced by about 17 per cent. Dams maintained on 5 μc Sr^{90}/gm. Ca or less did not differ substantially from the control mice in survival time or in disease incidence during these 525 days. The median life span of mice exposed to 10 μc Sr^{90}/gm. Ca since conception was reduced by about 41 per cent. A decrease in survival time was also apparent among the mice reared on 5.0, 2.5 and 1.0 μc Sr^{90}/gm. Ca since conception.

Tumors that can be attributed to radiation have appeared only among those mice maintained throughout life on 10 μc Sr^{90}/gm. Ca. Besides an increase over the normal incidence of tumors of the blood forming tissues, there have been epidermoid carcinomas of the oral cavity, osteolytic tumors of the skeleton, and osteogenic sarcomas. The osteogenic sarcomas appeared much later and in much smaller number than had been expected on the basis of previous experience with mice that had been injected with Sr^{90}. Since the major difference between a single injection and continuous ingestion concerns the dose rate, it appears that the amount of radiation absorbed per unit time is an important factor in the neoplastic process. In addition, the delay in the appearance of osteogenic sarcomas until the mice were approximately 450 days old suggests that very young mice are not necessarily more sensitive to a radiocarcinogenic stimulus than adult mice.—*Walter H. Jarvis, Jr., M.D.*

Ferrebee, J. W., and Thomas, E. D. Transplantation of marrow in man. *A.M.A. Arch. Int. Med.*, Oct., 1960, *106*, 523–531. (From: Mary Imogene Bassett Hospital, Cooperstown, New York.)

In this emerging age of nuclear medicine and possible nuclear warfare, much interest has been awakened in the transplantation of human tissue, and especially bone marrow. Partial successes have been obtained in thwarting lethal effects of radiation exposure with marrow transplants in animals. To date, this has not been so in man.

In general the tissues of one person do not flourish in the body of another. Genetic differences in the chromosomes of host and donor predetermine differences in their cellular constituents, presumably at the molecular level. These differences excite an immunologic response. Except in identical twins, a graft is recognized by the defense system of the recipient as possessing foreign antigens. The lymph centers react accordingly, and the transplanted tissue is subjected to round cell infiltration and inflammatory change. In a week or two the graft is rejected.

To suppress this graft versus host reaction, two methods have been explored experimentally in producing chimeras, that is, individuals in whom cells of different genotypes are tolerated. The first involves active acquisition of tolerance by the host for the graft. The second requires the destruction of mature lymph tissue and bone marrow by radiation followed by the engraftment of lymphopoietic and hematopoietic tissue from a suitable donor. The first method is not applicable to adults or even infants, and the second method is fraught with difficulties of the immune reaction itself.

Some success is obtained if fetal immunologically immature hematopoietic tissue is infused. If mature bone marrow is used, the marrow function is quickly restored, but the injected lymphocytic cells respond rapidly to produce granuloma formation, plasma cell accumulation, fibrinoid change, necrosis, and hemorrhage in the lymph nodes and spleen. The basic question is whether the harmful effects of the reactive lymphocytic cells outweigh the lifesaving effects of the erythroid, myeloid, and megakaryocytic elements.

No evidence of harm from marrow infusion has been seen in the few normal subjects whose radiation injuries have been treated by this means. However, most leukemic patients treated by this method after extensive radiation exposure have exhibited definite graft versus host reactions, although the leukemia itself remained in remission.

It has been found that, by irradiating the elements to be infused with 500 to 1,000 r, the lymphocytic cells are deprived of their ability to divide and multiply. Presumably this does not alter the usefulness of the platelets, leukocytes, and erythrocytes. Efforts to refine irradiation techniques and chemotherapy to the extent necessary for cracking the individuality of man's pattern of immunologic self recognition are proceeding. It may be that successful homotransplantation is not an unattainable goal.—*Arch H. Hall, M.D.*